A clinical guide to NEUROPATHIC PAIN

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- Did the drug affect one particular quality of pain? For example, sharp, lancinating/electrical, burning, aching, or skin sensitivity? The Neuropathic Pain Scale (table 4) can be used to help ascertain a patient's treatment response.
- Did you experience any side effects?
- Were these side effects tolerable or intolerable?
- Did these side effects subside as the medication was continued?

If the patient experienced less than "a lot of relief" and no side effects or tolerable side effects, the drug should be increased to the next higher dose. If the patient experienced intolerable side effects, the drug should be discontinued. If the side effects were tolerable and diminished over several days, the dose may be gradually titrated further.

Recommended treatment algorithm

As with all other medical conditions, the order in which drugs are prescribed for neuropathic pain should be based on 3 variables: proven efficacy, tolerability, and safety. The balance of these critical variables for a given medication, based on published controlled clinical trials and clinical experience, will help provide its rank order in a recommended treatment algorithm. Thus, using the above principle, the drug that is most likely to provide the best balance of pain relief and side effects will receive a higher ranking. As described below, although many medications have been shown to relieve neuropathic pain in some patients, a number of these drugs can potentially cause significant and even serious side effects.

Medication classes

Currently, the drugs prescribed to treat neuropathic pain (table 5) are classified as:

- Topical analgesics
- Adjuvant analgesics
- Opioid analgesics

Topical analgesics

Unbeknownst to most healthcare providers today, the use of topical drugs is an ancient form of pain therapy. Centuries ago, Egyptians and Chinese began applying medication directly to the skin of a painful body region in order to produce analgesia. Interest in topical drugs has increased in recent years, and in 1999 a topical lidocaine patch became the first drug approved by the US Food and Drug Administration (FDA) for the treatment of postherpetic neuralgia, a common neuropathic pain syndrome.

It is imperative to differentiate true topical medications from transdermal medications. As shown in table 6, there are significant differences among topical and transdermal drugs.

A true topical analgesic has the following characteristics:

- The medication is applied directly to the skin overlying the painful region.
- The medication penetrates the skin effectively.
- The site of the mechanism of action is local activity in the peripheral tissues, such as the peripheral nociceptors in the skin.
- No clinically significant systemic blood levels can be measured.

Topical drugs have the potential to be excellent medication for peripheral neuropathic pain syndromes, such as PHN, polyneuropathy, neuroma, and CRPS. In clinical practice, several advantages are inherent in topical drug delivery over oral agents, including:

- Lack of systemic side effects
- Lack of drug interactions

Table 6. Topical vs transdermal drug delivery

	Topical	Transdermal
Application site	Directly on painful skin	Distant from painful region
Site of activity	Local (peripheral soft tissue, nerve)	Systemic
Serum drug concentration	Insignificant	Necessary
Systemic side effects	Unlikely	Yes
Titration needed	No	Yes
Drug interactions	No	Yes

therapeutic concentration used to treat cardiac arrhythmias (figure 4).

Clinical trials and clinical experience. Controlled clinical trials have demonstrated that the lidocaine patch significantly relieves pain and allodynia in the majority of PHN patients when placed directly over the painful region. Anecdotal experience also suggests that this drug may be beneficial for other peripheral neuropathic pain syndromes, including painful polyneuropathy, such as diabetic and human immunodeficiency virus (HIV) neuropathy, postmastectomy pain, post-thoracotomy pain, and CRPS.

Acute side effects. The lidocaine patch may cause a localized minor skin irritation at the application site. Such reactions are generally mild and transient, resolving spontaneously within minutes to hours.

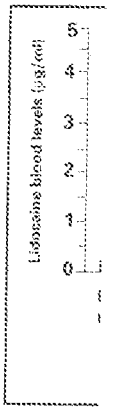

Figure 4.

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XIV PAIN

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Definition

For centuries, an accurate definition of pain has been elusive. In biblical times, pain and suffering were looked upon as a divine punishment for transgression.[1] It was not until 1973, when an international group of experts met for what would become the International Association for the Study of Pain (IASP), that a definition was put forth that emphasized the complex nature of pain: a physical, emotional, and psychological condition.[2] It is now recognized that the intensity of pain does not necessarily correlate with the degree of tissue damage present.[3]

Failure to recognize the complex factors that affect the experience of pain and reliance solely upon physical examination findings and objective laboratory tests may lead to the misunderstanding of pain and may result in the undertreatment of pain. Failure to understand the complex biologic, psychological, and social nature of pain may cause the clinician to disbelieve the patient's self-report of pain. Moreover, in medical school and during residency training, physicians are poorly instructed regarding the assessment, diagnosis, and treatment of pain. A recent survey of American neurologists clearly demonstrated the need for better education and training regarding pain.[4] Thus, the unfortunate fact is that pain of all causes continues to be poorly treated in America.

Very recently, medical organizations in America have responded to the need for better pain management. A national organization has developed pain standards based on input from the medical and lay communities and through consensus building; these standards acknowledge patients' rights to have their pain assessed, treated, and managed. This organization has begun to use these standards to ensure that principles of pain management are assimilated into hospitals' standards of care. Moreover, the legal system is setting precedents through judgments that establish untreated or undertreated pain as unacceptable. Through these activities, it is hoped that pain will be adequately understood and addressed so that patients will be better able to obtain relief from their pain and suffering.

Despite continued poor clinical training, the past decade has brought enlightened understanding regarding the complex physiology and pathophysiology of pain. It is an exciting time in the study of pain, as scientists are advancing the understanding of pain anatomy, physiology, and pharmacology by delineating varied, novel mechanisms that support the often complex clinical presentations of patients with pain. Moreover, for the first time in history, the pharmaceutical industry has allocated resources for the identification and development of innovative medications to attack pain on the basis of these new scientific advances in the understanding of pain. On the basis of newfound chemicals, receptors, and peptides, drugs are being developed that affect pain transduction, transmission, interpretation, and modulation in both the peripheral nervous system (PNS) and the central nervous system.

Epidemiology

Pain is one of the most frequent causes cited as the reason for visiting a doctor. Studies have demonstrated that episodic or persistent pain, including low back pain, headache, and arthritis, is one of the primary reasons that patients access the health care system.[5] It is estimated that in the United States, the prevalence of chronic pain in the general adult population ranges from 2% to 40%.[6] Migraines are estimated to affect one in 10 adults.[7] In epidemiologic studies, the prevalence of low back pain has varied from almost 8% to 37%, depending on the population. Low back pain is reported by adults of all ages; in particular, patients between 45 and 60 years of age experience low back pain.[8] Currently, it is estimated that 40 million individuals are afflicted with musculoskeletal conditions, as determined by the National Center for Health Statistics; this number will continue to increase in the decades to follow.[9] Patients afflicted with malignant diseases generally report increasing pain as their disease progresses, and it is estimated that about 75% of cancer patients experience pain.[3] In addition, an estimated 72% of patients fear dying in pain.[10]

Lastly, the costs to society related to the symptom of pain are immense. Patients with chronic pain incur health care costs that range from $500 to $35,000 a year; these figures do not reflect the costs of surgical procedures, which are likely to dramatically inflate these estimates. The annual cost attributed to back pain, migraine, and arthritis is a staggering $40 billion.[11] This estimation does not include lost workdays, nor does it include associated compensation, which would cause this figure to grow tremendously, especially as the population ages.

Neurobiology and the Experience of Pain

Pain is a subjective experience that has both sensory and affective components. The experience of pain involves a series of complex neurophysiologic processes that have four distinct components: transduction, transmission, modulation, and perception. Transduction is the process by which a noxious stimulus is converted to an electrical impulse in appropriate sensory nerve endings. Transmission is the conduction of impulses that arise from the painful stimulus along nerves to the CNS; major connections for these nerves are in the dorsal horn of the spinal cord and in the thalamus, with projections to the cingulate, insular, and somatosensory cortexes. Modulation alters pain transmission. There is evidence of both inhibitory and excitatory mechanisms that modulate nociceptive impulse transmission in both the PNS and the CNS.[12] Pain perception probably lies at the level of the thalamus, with the cortex being essential for the discrimination of specific sensory experiences.[11,13,14] Not all of these steps need to occur for a person to experience pain. For example, trigeminal neuralgia is thought to be caused by midaxonal discharges initiated at the site of a compressed or demyelinated nerve; this process occurs in the absence of transduction of a chemical stimulus at a nociceptor. As another example, modulation of a pain impulse may not occur if specific nervous system tracts are injured. In fact, in phantom-limb pain, the limb in which the pain is experienced does not even exist. Thus, one may experience pain without nociception or even in the absence of nociceptors (pain receptors).

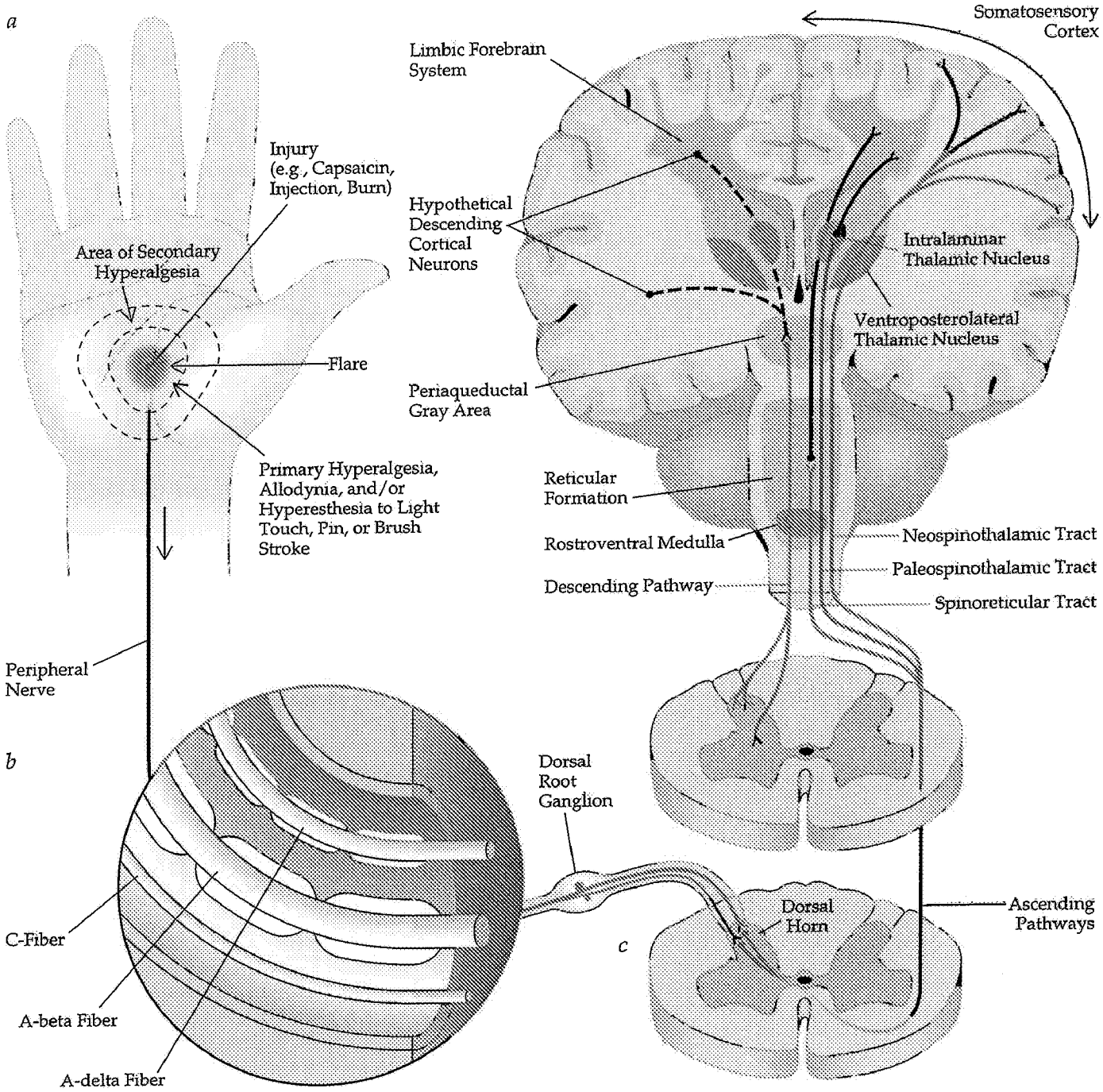

Figure 1 **(*a*) Stimulation of C fibers by intradermal injection of capsaicin or thermal injury produces spontaneous pain and pain evoked by light touch at the site of injury (primary hyperalgesia). In addition, an area of allodynia (pain after noninnocuous stimulation) and secondary hyperalgesia (increased pain after a noxious stimulus) outside of the area of primary injury is produced by the activation of *N*-methyl-D-aspartate (NMDA) receptors in the central nervous system, which occurs as a consequence of the afferent nociceptive impulse traffic. (*b*) When activated by mechanical, thermal, and chemical stimuli, nociceptors conduct afferent impulses toward the spinal cord via A-beta (thinly myelinated) fibers and C (unmyelinated) fibers. A-beta (light touch) fibers may become sensitized by CNS mechanisms to produce allodynia. (*c*) When areas in the thalamus and cerebral cortex are activated, secondary projections in the spinothalamic tract, dorsal column tract, and other nociceptive pathways lead to the conscious perception of pain.**

PERIPHERAL NERVE PHYSIOLOGY

Pain Receptors

The peripheral matrix contains a plethora of neural structures, one type of which is responsible for detecting the presence of noxious stimuli resulting from chemical, thermal, or mechanical insult. In normal, uninjured tissue, nociceptors are inactive until they are stimulated by sufficient energy to overcome their stimulus (resting) threshold. In this way, the nociceptor serves as a first-line defense against random signal propagation to the CNS for interpretation as pain. Threats to the integrity of this function may compromise the screening ability of the nociceptor and thus create further problems [*see Figure 1*].

Nociceptors react to different types of stimuli. Some C-nociceptors, for example, react only to heat or cold stimuli, whereas others react to multiple stimuli (e.g., chemical, heat, and cold).

The same is true for A-delta nociceptors. Other receptors respond to stimuli in specialized ways. Some A-beta receptors have nociceptor-like activity; in addition, A-beta mechanoreceptor sensory fibers can be recruited to transmit signals that will be interpreted as painful when their environment is engulfed by inflammation and its by-products. Mechanical allodynia (e.g., a painful sensation arising from the pressure of clothing on skin or a sensation of burning caused by a light touching) results from this type of A-beta mechanoreceptor recruitment.[15]

Transduction and Transmission

When the resting threshold of nociceptors is surpassed, mechanical, thermal, or chemical energy is converted into an electrical action potential (transduction) capable of propagating (transmission) along the nerve fiber toward the spinal cord. Action potential propagation occurs through the opening and closing of sodium and potassium channels. The generation of only one action potential is sufficient to elicit a response. Nociceptors may detect such a stimulus and generate an action potential that results in the perception of pain even if the tissue is not damaged. This firing of the nociceptor before the actual bodily insult is an important protective function; we have all, upon touching a hot object, felt pain and then moved our finger from that object before tissue damage occurred.

In addition to the generation of an action potential, there are a number of other events that occur after detection of a noxious stimulus. The acute inflammation that develops in response to tissue injury serves to protect injured tissues and promote healing. A number of inflammatory mediators are released, such as bradykinin, prostaglandins, serotonin, histamine, cytokines, eicosanoids, neuropeptides, purines, and protons. Bradykinin is believed to be the first mediator to cause activation of second messengers, resulting in increased sodium channel conductance and sensitization. Prostaglandins enhance bradykinin activity; hence, they contribute greatly to inflammatory processes and have long served as targets for pharmacologic treatments. Other substances that cause cellular breakdown are released and subsequently surround neural structures. Exposure to inflammatory mediators causes A-delta fibers and C-fibers to undergo peripheral sensitization, whereby their stimulus thresholds are reduced, and receptor firing and intensity is increased and prolonged; this results in an increase in the frequency of pain signals transmitted into the CNS. In normal situations, these physiologic alterations caused by the inflammatory process are limited. Thus, in the vast majority of cases of acute inflammation, the process naturally resolves as the tissue heals; peripheral sensitization vanishes as nociceptors return to their original stimulus (resting) threshold and the CNS no longer receives pain signals. However, chronic pain can occur when, for unknown reasons, the pathologic conditions associated with the inflammatory process do not resolve; this leads to a continual increase in pain sensations resulting from normally painful stimuli (hyperalgia) and the occurrence of pain sensations in response to normally nonpainful stimuli (allodynia). Less often, a chronic inflammatory process facilitates an ongoing peripheral sensitization and hence leads to chronic pain.

Neuropathic pain is a more distinct type of chronic pain that occurs in the complete absence of an inflammatory reaction. In neuropathic pain, there is direct damage to the peripheral nerves, which results in a continual ectopic spontaneous discharge of pain signals. In addition, the bodily region becomes sensitive to stimulation (e.g., ionic, mechanical, or thermal), resulting in severe chronic pain, hyperalgesia, and allodynia.[15] Peripheral sensitization can contribute to the development of secondary hyperalgia and central sensitization.

There are two primary nerve fibers responsible for carrying pain signals toward the spinal cord. They differ in their morphology and physiology and have different rates of transmission and sensations. As previously stated, A-delta nociceptors and C-fibers innervate all tissues and reside alongside other sensory and autonomic neurons. A-delta fibers are thick, myelinated fibers. The myelination of the axon provides for junctions that allow the pain signal to jump, resulting in rapid pain-signal transmission. Alternatively, C-fibers are thin, unmyelinated fibers that require the action potential to travel along the full axonal length to arrive centrally, resulting in slower propagation. A-delta fibers are responsible for the brief, sharp, initial pain. This specialization, which results in the ability to detect dangerous mechanical or chemical insults, makes A-delta nociceptors residing in the skin of tremendous value in alerting an individual of harm and preventing further damage by providing for a reflexive and rapid response. Often, a second pain follows shortly, which is dull, achy, and unpleasant; such pain is the result of C-fiber transmission.

CENTRAL NERVE PHYSIOLOGY

Although presented here in a simplistic, static manner, pain transmission from peripheral structures to the spinal cord and eventually to the higher centers of the CNS is a dynamic process involving several pathways, numerous receptors, neurotransmitters, and secondary messengers. This discussion provides an overview of the primary, most well-known components and processes.

The Dorsal Horn and Ascending Nociceptive Pathway

Structures The primary afferent fibers, with their cell bodies lying in the dorsal root ganglion, connect with a second neuronal cell, located in the dorsal horn of the spinal cord. Afferent fibers from nociceptors enter the spinal cord laterally in the dorsal root and ascend or descend several segments in the Lissauer tract before synapsing in the dorsal horn.

The dorsal horn consists of six laminae. Laminae I and II are the sites of termination of primary afferent C-fibers; together, they make up the substantia gelatinosa, which is important for integration and modulation of incoming nociceptive information.[16] Lamina V is the site of second-order wide dynamic range (WDR) and nociceptive-specific (NS) neurons, which receive input from both nociceptive and nonnociceptive primary neurons. The NS neurons respond only to intense noxious stimulation in the peripheral receptive field; the WDR neurons respond to innocuous and noxious stimuli of many types. Both types of neurons are thought to be important in the encoding of nociceptive information: the NS response signals the presence or absence of a tissue-damaging stimulus, whereas the WDR response provides information about stimulus quality and perhaps location. A variety of chronic-pain states can be explained in terms of the inputs to these cells and their supraspinal connections.

Transmission and modulation The dorsal horn and its laminae serve as the backdrop for the wealth of activity initiated on the arrival of the action potential from the periphery via the primary afferent neuron. As described (see above), primary afferent neurons terminate in the dorsal horn and synapse with secondary afferent neurons. These secondary neurons are in-

formally referred to as gate cells because of the important role they have in the initial modulation of action potentials in the dorsal horn. The gate cells are involved in screening action potentials by determining which action potentials continue to be transmitted to the higher centers of the brain for perception. They are involved in determining which action potentials result in reflex action that serves to move the tissue away from the noxious stimulus and avoid further insult. The involvement of inhibitory interneurons that release neurotransmitters such as γ-aminobutyric acid (GABA), which also have receptors on the secondary afferent neuron and produce inhibitory postsynaptic action potentials, counteracts the transmission of the excitatory action potential received from the primary afferent neuron. This gate cell function determines the nature of excitation and inhibition action potentials and the resultant effect on further signal transmission.

Under normal conditions, secondary afferent neurons are not spontaneously active; rather, they are activated by an action potential generated in the periphery. Much like the nociceptor in the periphery, these cells have a specific purpose (i.e., to regulate incoming action potentials) and have a stimulus threshold that must be overcome. After depolarization, the gate cells repolarize and return to the stimulus threshold in preparation for future activity.

Glutamate, among other amino acids and peptides, is released from presynaptic membranes of the primary afferent neurons terminating in the dorsal horn. It is an excitatory amino acid and has the ability to activate numerous receptors such as kainate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors. For example, the action of glutamate on AMPA receptors causes a rapid depolarization of the secondary afferent neuron membrane; if the threshold is met, an action potential is generated. In addition, the binding of glutamate can result in the activation of cascades of enzymatic processes and second messenger systems, some of which have been shown to be involved in nociception and may be responsible for the initial pain modulation that can occur in the spinal cord. Much like the peripheral mediators described earlier (e.g., bradykinin), glutamate acts as a central pain mediator at nearly all secondary afferent neurons involved in nociceptive processing in one way or another; thus, it is the main neurotransmitter in primary afferent neurons.[17,18]

NMDA receptors and central sensitization NMDA receptors are located on the secondary afferent neuron, or postsynaptic to the primary afferent neuron. Their ion channel is blocked by a magnesium ion. Under normal circumstances (i.e., stimuli caused by acute injury), the secondary afferent neuron is not depolarized long enough to allow the magnesium ion (acting like a stopper) to be dislodged to permit calcium ions to cross the channel, even if glutamate is bound to it. Glutamate is rapidly removed from the synaptic cleft; hence, there is no activity at the NMDA receptor in normal nociceptive transmission processes [*see Figure* 2].

In the presence of abnormal painful conditions (e.g., pain arising from persistent acute injury or peripheral sensitization, neuropathic pain, or chronic pain), the frequency of pain signal transmission increases. Glutamate is first released into the synaptic cleft and is then removed. Presynaptic release then continues as a result of the increased frequency of pain signal transmission. This process results in a persistent net increase in the amount of glutamate available in the synaptic cleft. Thus, secondary afferent neurons are depolarized long enough for the magnesium ions blocking NMDA receptors to be dislodged. The result is activation of NMDA receptors. Activated NMDA receptors serve to activate secondary messenger and enzymatic processes (as a result of calcium ion influx into the secondary afferent neuron) that are believed to contribute to sustaining enhanced neuronal sensitivity (e.g., central sensitization).[17,19]

The occurrence of central sensitization is believed to be the crux of many chronic-pain states, particularly those that are classified as neuropathic.[17] Central sensitization describes increased excitability of secondary afferent neuron membranes, evoked by the neurochemical changes resulting from NMDA receptor activation. In turn, the increased excitability of the membranes of secondary afferent neurons changes the subsequent response of these second-order neurons to future input.[17] An increase in the number of action potentials generated by peripheral C-fiber input is referred to as wind-up; however, in general, the terms central wind-up and central sensitization are used interchangeably to describe the same phenomenon. Secondary afferent neurons respond more easily and more vigorously to the inputs received from C-fiber–associated receptors that come from either damaged or sensitized nociceptors or from low-threshold mechanoreceptors. Large and prolonged input from sensitized nociceptors resulting from inflammation or spontaneous discharge associated with nerve injury cause a chronic state of central sensitization.[15] Thus, an important component of many chronic-pain conditions is central sensitization resulting from chronic PNS input into the spinal cord; NMDA receptors play a critical role in this process.

Central sensitization results in the compromise of the secondary afferent neurons in a manner similar to that in peripheral sensitization. Compromised secondary afferent neurons possess lower stimulus thresholds and undergo sensitization (that is, receptor firing and intensity is increased and prolonged); in addition, spontaneous and ectopic signal generation occurs. Contributing to the problem is the fact that these secondary afferent neurons are no longer able to track and regulate postsynaptic action potentials.[17] Hence, the gatekeeping traits of secondary afferent neurons are lost, leaving the excitatory aspects of pain transmission unopposed. This results in the spontaneous generation of pain signal and exaggerated nervous system responses to sensory stimuli (secondary hyperalgia and allodynia).[17] Because higher levels of the brain cannot discern the origin of the pain signals, the patient is in a continual state of pain that is often associated with an abnormal sensitivity to stimuli.

The point at which normal events associated with acute pain responses become transformed so as to produce pathologic chronic pain and the point at which the activity occurring at the dorsal horn causes secondary afferent neurons to become locked in a chronically sensitized state are unknown. Furthermore, it is not known why this abnormal nervous system state associated with chronic pain occurs in certain individuals only after certain injuries and other bodily events. Dysfunction of the secondary afferent neuron resulting from these neuroplastic changes can be perpetuated indefinitely, irrespective of the presence or absence of continued peripheral sensitization; it may also result in the phenomenon of phantom pain, in which the patient experiences pain associated with a limb that is no longer present as a result of amputation or of its having been severed. This is particularly true if the input is a result of ectopic and spontaneous action potential generation caused by nerve injury. Although it is unclear at this time why neuroplastic changes initiate central sensitization, it has been definitively shown that the NMDA receptor has

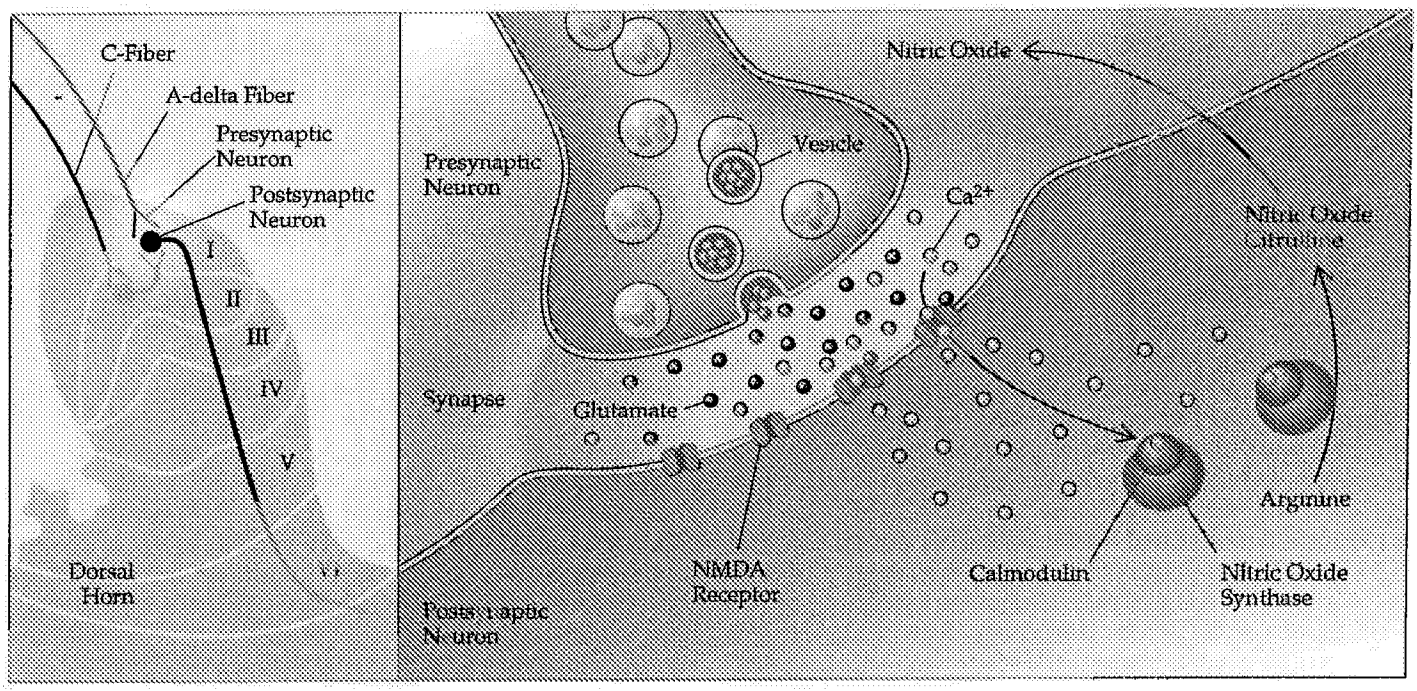

Figure 2 **The spreading flare of pain, allodynia, and hyperalgesia is explained by activated NMDA receptors in the spinal cord dorsal horn. Activation of these receptors, increasing calcium conductance, leads to activation of protein kinases and to activation of the enzyme nitric oxide synthase, which ultimately leads to nitric oxide synthesis. These actions also depend on activation of cyclic guanosine monophosphate (cGMP) and other secondary messenger systems.**

a role in this process. In addition to facilitating central sensitization, the activation of the NMDA receptor leads to the initiation of a number of secondary messenger systems and the generation of various substrates (e.g., nitric oxide) that contribute to nociception and the development of opioid tolerance. NMDA pharmacotherapy is addressed later in this subsection.

Nonthalamic Tracts and Other Ascending Nociceptive Systems

The transmission of action potentials generated at the dorsal horn by secondary afferent neurons continues cephalad to the CNS when it is not impeded by inhibitory interneurons or the endogenous opioid system. It is important to note that signal generation may be the result of spontaneous ectopic firing at higher points along the pain pathways if neural injury occurs at areas beyond the periphery and the dorsal horn; this is seen in central neuropathic pain that is associated with damage to the spinal cord or brain.

The spinothalamic tract is often regarded as the prominent pathway for nociceptive neural transmission. Axons from WDR and NS neurons in laminae I and V decussate in the central gray matter of the spinal cord and become the ascending projections of the neospinothalamic and paleospinothalamic tracts. The neospinothalamic tract projects monosynaptically to the ventroposterolateral (VPL) nucleus of the thalamus and probably encodes for stimulus localization and intensity. The paleospinothalamic tract sends multiple projections to the brain-stem reticular formation and medial regions of the thalamus before termination in the VPL nucleus. Several other ascending spinal tracts are known to transmit nociceptive information to the brain; these include the spinohypothalamic tract, the spinoreticular tract, the spinopontoamygdala tract, and the dorsal column tract.[20] The spinoreticular and spinocervicothalamic tracts ascend in the ipsilateral dorsolateral quadrant (separate from the spinothalamic tracts in the anterolateral quadrant) but join with the spinothalamic tract in the medial lemniscus in the brain stem. Dorsal column fibers transmit both proprioceptive and nociceptive information[21] and ascend in the ipsilateral medial lemniscus to the thalamus; stimulation of these fibers is a target for pain relief.[22] It has been suggested that alternative pathways such as the dorsal column tracts assume a more central role in the recurrence of painful symptoms after relatively selective ablative procedures on the spinothalamic tract (e.g., cordotomy).

Pain from head and neck structures is processed through cranial nerves V, VII, and IX and the first three cervical spinal nerves, which are considered part of the PNS. The spinal trigeminal nucleus and adjacent reticular formation are the equivalent of the spinal dorsal horn. This nucleus has laminar structure and afferent synaptic connections similar to those of the spinal dorsal horn. Second-order neurons send axonal projections to the other side of the brain stem, where they ascend in the contralateral medial lemniscus, eventually terminating in the ventroposteromedial (VPM) thalamic nucleus. The ventrobasilar complex (VPL, VPM) axons project to the parietal somatosensory cortex; the medial thalamic nuclear groups project to the striatum and cerebral cortex.

Thalamus and Cerebral Cortex: Perception and Discrimination

After leaving the dorsal horn and ascending via the pain pathways described above, nociceptive action potentials reach the higher centers of the brain, which include the reticular formation and midbrain of the brain stem, the thalamus, the hypothalamus, and the cerebral cortex. The nociceptive inputs are received at these levels, where they assume qualitative and quantitative characteristics. Each area contributes to the development of the pain experience and subsequent action or reaction to it. These areas function to alert the individual to the pain and its accompa-

nying dangers, alleviate pain through natural pain modulation processes, and reduce and prevent further tissue damage. Emotions are activated and heightened, as is awareness of location and pain intensity of the injured area. Additionally, autonomic function, motor function, and descending modulating pain pathways respond as a result of activity in this central complex of structures. It is believed that multiple complex brain systems are automatically involved when a pain signal reaches the brain; these systems include nociceptive, motor, orientation, motivation, affect, and autonomic systems.[23] Interestingly, these distinct yet interactive brain systems share many brain structures.[23]

Nearly a century ago, Head and Holmes postulated that the thalamus and cortex were essential for pain perception and discrimination, respectively.[14] It was believed that the cortex did not have much involvement in pain perception because patients continued to experience pain despite their affliction with cortical injury, tumors, or disease. These afflictions do, however, alter the detection and discrimination of pain stimuli.[24] Penfield's classic cortical mapping studies demonstrated that cortical stimulation produces pain, though infrequently.[25] Patients with lesions of the insular cortex may manifest a syndrome called pain asymbolia. Patients with this disorder do not generate emotional pain responses despite normal thresholds to cutaneous pain stimuli contralateral to the insular lesion.[26] Further support for the specific role of the cortex in the perception and processing of painful stimuli comes from animal studies that demonstrate NS neuronal responses identical to those found in the spinal cord dorsal horn.[27,28]

A lesion anywhere in the spinothalamic tract and thalamocortical projections may result in central pain. Hypoalgesia, the reduced appreciation of painful stimuli, such as pinprick or thermal sensation (especially cold), almost invariably accompanies central pain disorders. Postulated mechanisms for hypoalgesia include a loss of inhibitory influences on excitatory pathways and the emergence of spontaneous thalamic activity (primarily in VPL and VPM) in patients with central pain syndromes after stroke.

Brain imaging with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) enables visualization of cortical and thalamic structures associated with processing of experimental and natural pain stimuli. The cortical and subcortical areas that are activated depend on the type of pain stimulus. In general, brain-imaging studies in humans demonstrate consistent activation of the thalamus, anterior cingulate gyrus, and insular cortex.[29,30] Primary and secondary somatosensory cortices are less consistently activated.[31] The PET studies, however, indicate that the areas of cortical activation seen in experimentally induced pain do not necessarily match those in patients with chronic neuropathic pain.[32]

It is important to realize that the physiologic reactions in healthy volunteers appear not to correlate specifically to the complexities involved in human chronic pain conditions. PET images show that in healthy persons who are subjected to experimentally induced pain, regional cerebral blood flow in the contralateral posterior thalamus is consistently decreased. By contrast, increased regional cerebral blood flow is observed in the bilateral anterior insular and posterior parietal cortices, bilateral inferior lateral prefrontal cortices, and cerebellar vermis.[29]

The anterior cingulate cortex has long been recognized as a region of pain perception; lesions within this region result in diminished pain. This area of cortex receives major input from the medial thalamus. Recent evidence from PET studies has confirmed the crucial role of the anterior cingulate cortex in subserving the affective components of the pain experience.[33] The anterior cingulate cortex is selectively activated by painful thermal stimuli.[30,32] Metabolic activity is attenuated in the anterior cingulate cortex when patients are subject to psychological techniques that produce analgesia, such as hypnosis and active distraction.[33] Interest in the cingulate cortex as a neuroablative target for intractable pain is based in part on observations suggesting that the cingulate cortex plays a key role in the processing of nociceptive information.[34]

Endogenous Pain Suppression Pathways: Further Modulation

Descending pain pathways are activated as a result of pain detection, discrimination, and perception at the higher levels of the CNS (see above). Inhibitory and excitatory neuroanatomic pathways originate in the brain stem ventoreticularis median nucleus and descend in the dorsal longitudinal fasciculus to modulate nociception and pain perception.[35] These pathways are activated by stress as a result of exercise, sexual stimulation, and battlefield exposure; once activated, they keep noxious stimuli from interfering with the activity. Several important neurotransmitters have been identified in these descending pathways, including norepinephrine, serotonin, and endogenous opioid compounds (e.g., methionine-enkephalin, leucine-enkephalin, and β-endorphin).[12] The inhibitory pathways involve the off cells, which are activated by opioids; the excitatory pathways involve the on cells, which are inhibited by morphine. The relative activity of on and off cells determines the degree of inhibition occurring in this endogenous pain suppression pathway.[35] This mechanism is thought to provide the physiologic basis for the action of morphine and other opioids, as well as other analgesic drugs, such as tricyclic antidepressants (TCAs) and alpha-adrenergic agonists.

TCAs, such as amitriptyline and desipramine, block the presynaptic reuptake of serotonin and norepinephrine and thus augment their postsynaptic actions in descending pain suppression pathways.[36] TCAs have been shown to have analgesic activity independent of their antidepressant effects, especially in such neuropathic pain states as diabetic neuropathy and postherpetic neuralgia.[37]

Alpha$_2$-adrenergic agonists active at adrenergic receptors in the spinal cord (e.g., clonidine) produce analgesia on administration into the epidural space.[38] Phentolamine, an alpha$_2$-adrenergic receptor antagonist, has also been used to manage pain in patients with regional pain syndromes, particularly when sympathetically maintained pain is suspected. The effect of phentolamine may be predictive of responsiveness to anesthetic sympathetic blockade.[39]

Activation of this descending pathway by the action of endogenous opioids may account for the phenomenon of placebo and acupuncture analgesia.[12] The inconsistent reversibility of placebo and acupuncture analgesia by opioid antagonists (e.g., naloxone) casts doubt on this theory, however. As with other aspects of pain, the activation of the descending pathways is complex, and continued elucidation of the mechanisms involved will help to better define the clinical role and significance of this system as well as identify new targets for pharmacotherapy.

Classification of Pain

No two patients will have the same experience of pain. Each person who experiences pain does so in a unique, individual way, even if the physical injury is identical to that afflicted upon another. The presence of fear, anxiety, depression, anger,

Table 1 Physiologic Pain Categories

Type of Pain	*Examples*	*Putative Mechanisms*
Nociceptive	Arthritis, fracture, bone metastasis, cellulitis	Activation of nociceptors
Visceral	Pancreatitis, peptic ulcer, myocardial infarction	Activation of nociceptors
Neuropathic	Postherpetic neuralgia, diabetic neuropathy, poststroke pain, trigeminal neuralgia	Ectopic discharges within nervous system; spontaneous activity in nerves; neuroma formation; other
Complex regional pain syndromes[10]	Persistent focal pain after trauma with or without evidence of sympathetic involvement	Sensitization of spinal neurons; ephaptic transmission; other

and fatigue can affect the way in which pain is perceived. For example, the death of a loved one may affect the way in which concurrent pain secondary to an injury is perceived. Patients may have a difficult time articulating what the experience is like for them. Although the patient's self-report is the cornerstone of pain assessment, the subjective nature of painful experiences can make it difficult for a clinician to categorize a patient's pain on the basis of that patient's description. Without a means of organizing the information provided by the patient, clinicians may struggle to understand what the patient is trying to communicate.

The subjectivity of pain can make it difficult to recognize and understand pain mechanisms and the way in which current treatment approaches work. Moreover, subjectivity makes discussion of pain among members of the health care team and between clinicians and researchers difficult. Historically, terms used to discuss pain varied in meaning and application; this contributed to problems in communication. In recent years, however, the IASP has attempted to standardize pain vocabularies and classification systems to establish a common language with which to address the problems inherent in the subjective nature of pain.

This subsection considers pain with regard to time (acute pain versus chronic pain) and pathophysiology (nociceptive pain versus neuropathic pain) [*see Table 1*]. Although pain can be categorized in terms of etiology by considering pain to be a symptom of disease process or injury or by considering pain to itself be a disease, we feel these considerations can be accommodated in the context of the aforementioned categories.

NEUROPATHIC AND NOCICEPTIVE PAIN

The description of pain in terms of underlying pathophysiology generally involves distinguishing nociceptive pain from neuropathic pain. Neuropathic pain results from damage to peripheral or secondary afferent neurons or damage to higher levels of the CNS that results in abnormal signal generation (e.g., ectopic or spontaneous), propagation, or perception. Although idiopathic origins are possible, neural damage usually results from iatrogenic causes (e.g., surgery, radiation, or as a side effect of medications such as chemotherapeutic agents or antiviral agents used to treat HIV infections) or from disease processes (e.g., tumor infiltration and compression or stroke). Patients may describe neuropathic pain as burning, stabbing, or tingling. Other words descriptive of neuropathic pain include hot, cold, raw skin, itchy skin, dull, and achy. Patients may have both deep involvement and surface skin involvement. The Neuropathic Pain Scale has been designed to assess specific qualities of neuropathic pain.[40] Medications that interfere with signal propagation are useful in addressing many conditions involving neuropathic type pain; such medications include TCAs, anticonvulsants, local anesthetics, and opioids. Medications that target activity at the dorsal horn (e.g., NMDA receptor antagonists) may also be helpful in treating neuropathic pain.

As its name indicates, nociceptive pain results from the activation of pain receptors by noxious stimuli. This type of pain can be further analyzed in terms of somatic and visceral components, which somewhat differentiate the location of the activated receptors. Somatic nociceptive pain originates from deep tissue injury or cutaneous injury, whereas visceral nociceptive pain arises from injury of an organ system (either the organ itself or the pleura/peritoneum). Somatic pain is often easily localized and is described as dull, achy, or gnawing. Deeper somatic pain resulting from injury to muscles and joints may be less easily localized. Examples of somatic nociceptive pain include pain associated with bone fractures and muscle pulls. Universally, visceral pain is described as diffuse, dull, achy, and gnawing. It is poorly localized and radiates from its location. Examples of visceral nociceptive pain include pain caused by bowel obstructions and the infiltration of tumors into organs. Both types of nociceptive pain are responsive to common analgesic medications outlined in the World Health Organization analgesic ladder; these medications include nonopioid agents, such as acetaminophen and ibuprofen, and opioid agents.

ACUTE AND CHRONIC PAIN

The most common reason why individuals seek health care is for treatment of acute pain. Actual or potential tissue damage or injury initiates the pain process. Acute pain is generally associated with well-defined tissue damage, and the pathology is generally readily apparent. It is limited in duration, and it is not usually associated with long-term effects upon the patient's quality of life or with progressive disease. After a relatively limited healing period, which ranges from hours to days, the pain receptors involved return to a normal resting stimulus threshold. Examples of acute pain are tissue injury resulting from trauma or surgery. Treatment approaches include common analgesic medications (e.g., opioids and nonopioids).

Chronic pain can be categorized as malignant or nonmalignant. Malignant chronic pain usually has pathology present and is indicative of a life-limiting disease such as cancer, end-stage organ dysfunction, or HIV infection. It may have both nociceptive and neuropathic elements; therefore, opioid, nonopioid, and adjuvant agents may be necessary for treatment. Chronic nonmalignant pain may also be present for months to years and can be sporadic. Often there is no detectable pathology because the injured area in question is often physically remote from the original area of stimulation. Additionally, neuroplastic changes that

may have occurred in remote locations (e.g., the dorsal horn of spinal cord) make detection difficult. Chronic pain often begins in a manner similar to acute pain; why it is perpetuated is not clearly understood, although inroads are being made in our understanding. Examples of chronic nonmalignant pain include low back pain, headaches (migraine and others), arthritis, postherpetic neuralgia, and diabetic neuropathy.

Patients with acute pain and patients with chronic pain alike may exhibit autonomic signs and symptoms when pain is present. These signs and symptoms may include tachycardia, elevated blood pressure, rapid breathing, increased sweating, and anxiety. Patients may guard the painful site; guarding is more common in patients with chronic pain who have allodynia or who for unknown reasons experience sudden spontaneous exacerbations of their pain. It is important to remember, however, that the presence or absence of autonomic signs and symptoms does not provide the clinician with a shred of evidence that pain is or is not present. The vital signs of cancer patients may not suggest that pain is present despite the patient's verbalization to the contrary. Clinicians should not rely on the presence or absence of tangible signs and symptoms when determining a course of treatment of pain.

The basic principles concerning autonomic signs and symptoms described above should be considered when evaluating patient behaviors. Behavior should not be used to determine the intensity of pain that a patient is experiencing. Patients with acute pain may grimace or guard the painful area, and they may have a degree of anxiety that diminishes as the injured area heals. Patients with chronic pain may or may not exhibit these behaviors; more commonly, patients with chronic pain have a resigned or flat affect. Pain may cause social dysfunction, whereby patients do not feel like interacting with others or stop verbalizing how they are feeling because it does not provide them any relief. Family members and health care professionals may not believe the patient; therefore, the patient may give up trying to be heard. Anxiety and depression are not uncommon in patients, because pain dominates their lives; this is particularly true if the pain is accompanied by loss of function and affects activities of daily living. When asked about when their pain began, many patients with pain are unable to do so. Worse yet, many patients are unable to remember a time when they did not have pain. It is imperative that health care professionals work to alleviate this terrible suffering.

Principles of Pain Assessment and Pain Management

The multifaceted, complex nature of pain poses numerous challenges for the clinician engaged in treating patients suffering from painful conditions. Knowledge of the different types of pain (as classified by pathophysiology or time course), the type

Table 2 Questions for Eliciting the Patient's Self-report Regarding Pain Intensity, Character, and Psychosocial Assessment Domains[3,50]

Parameter	*Suggested Questions*
Intensity and Character	
Onset	When did the pain start? What might be the cause of pain?
Duration	How long does the pain last?
Location	Where is the pain? Is the pain in one place or in multiple locations? Does it originate in one area and radiate to other areas?
Quality	How does the pain feel? Describe your pain for me. (Use the Neuropathic Pain Scale[53] if neuropathy is suspected.)
Intensity	On a scale of 0–10 (0 = no pain, 10 = pain at its worst), assign a number representing the pain now and at its worst.
Aggravating factors	What exacerbates the pain?
Alleviating factors	What relieves the pain?
Other prevailing symptoms	Are there any other symptoms present, such as numbness or weakness, involuntary movements, bowel or bladder dysfunction, insomnia, anxiety, or nausea?
Previous pharmacologic approaches	What medications have you tried for pain relief? How well did they work? Were there any problems associated with them (i.e., adverse events)? What is your current treatment plan? Was an adequate drug trial given for each medication (i.e., titrated appropriately)?
Other pain-management approaches	What other treatments have been tried and what were the outcomes?
Pain interference with activities of daily living	How are work and family responsibilities affected by the pain? Are there activities you are now unable to perform as a result of the pain? What activities would you like to work toward restoring (i.e., goal setting)? Suggest using the Wisconsin Brief Pain Questionnaire[52]
Complex regional pain syndrome suspected	In the painful region, are there abnormal skin color or temperature changes, swelling, sweating, or skin dryness?
Psychosocial	
Accompanying disease states or symptoms	Is the patient suffering from depression, anxiety, posttraumatic stress disorder? Is the patient under the care of a psychiatrist or psychologist or receiving medication to address these problems?
Coping mechanisms	How does the patient cope with the pain? How does the family cope with the patient?
Satisfaction	How satisfied is the patient with past treatments? How satisfied is the patient with professional health care support?
Feeling toward pain	What does pain mean to the patient and to the family?
Comfort with treatment approaches	What does the patient know about treatment approaches? What approaches does the patient prefer? What does the patient expect from treatment?
Concerns	What are the patient's concerns toward unrelieved pain, treatment approaches, health care providers, and access to medications?

Table 3 Pain-Assessment Mnemonics[42,50]

A	Ask about pain regularly; assess pain systematically
B	Believe the patient and family in their reports of pain and what relieves it
C	Choose pain-control options that are appropriate for the patient, family, and setting
D	Deliver interventions in a timely, logical, and coordinated fashion
E	Empower patients and their families; enable them to control their course to the greatest extent possible
P	Palliating or precipitating factors
Q	Quality of pain
R	Radiation of pain
S	Severity of pain
T	Temporal aspects of pain
U	The effect of pain on YOU

of pain most prevalent in specific disease states (e.g., the dull, achy, constant pain seen in breast cancer patients with metastases to bone, and the sharp, burning pain and skin sensitivity seen in patients with neuropathic pain), and the psychological sequelae of pain, as well as an understanding of the detrimental impact that pain can have on a patient's quality of life, enables the clinician to better care for patients in pain. In addition, knowledge of the tools and techniques of pain assessment and of pharmacologic and nonpharmacologic treatment approaches can help the clinician achieve pain relief goals.

PAIN ASSESSMENT

Pain is subjective and unique to each patient. Unlike with hypertension or diabetes, there is no biologic marker of pain; hence, there are no laboratory tests or objective diagnostic tools to detect the presence of pain, to assess the intensity of pain, or even to determine the source of pain. Thus, the most important tenet for any clinician who assesses and treats a patient in pain is trust—the patient reporting the symptom of pain must always be believed. The clinician must rely on and accept the patient's self-report of pain; to do otherwise is poor, if not unethical, medical practice.[41]

Assessment Tools

The patient's self-report of pain is the most accurate indicator of the existence and intensity of pain.[41] Patients should be queried as to the character, intensity, location, frequency, and duration of painful episodes, as well as to the presence of aggravating or palliating factors [*see Table 2*].[3] It is important to determine the temporal nature of pain (i.e., whether the pain is acute, chronic, or episodic) [*see Table 3*].[3,42] Further, there are a variety of reliable and valid pain-assessment instruments to quantify the intensity of pain and the degree to which pain interferes with the patient's activities of daily living; examples include the Wisconsin Brief Pain Questionnaire,[43] the Neuropathic Pain Scale,[40] the McGill Pain Questionnaire,[44] and visual analogue scales. In using these tools, patients are asked to rate their pain on a scale of 1 to 10: mild pain is indicated by a score of 1 to 4; moderate pain, 5 to 6; and severe pain, 7 to 10. These scores help clinicians categorize the intensity of their patients' pain or the degree to which pain interferes with their quality of life, and they provide a means of objectively ascertaining patients' responses to therapy. The information obtained through the patient's self-report of pain and through the routine use of validated pain-assessment tools can often initially guide a clinician in deciding on a particular treatment approach.[45] For example, pain that a patient describes as deep, sharp, and burning may immediately suggest that the pain is neuropathic in nature. A number of questionnaires allow a broader understanding of the impact that pain has on the patient's quality of life; such questionnaires elicit information on the patient's social, psychological, physical, and spiritual well-being. Examples of these broader assessment tools are the Medical Outcomes Study 36-Item Short Form (SF-36) and the Sickness Impact Profile.

Psychological Assessment

At the time of the initial pain assessment, it is critical to ask about psychological and psychosocial factors; these include the social, personal, and financial costs of pain, as well as the effect of pain on the family. Exploration of these areas is crucial to developing a comprehensive treatment plan.[46] Common comorbid psychiatric conditions in patients with chronic pain include depression, anxiety, and posttraumatic stress disorder.[47-49] The presence of clinical depression and avoidance behaviors and the degree of family or social support should be assessed; these factors may influence the meaning and perception of pain and may compromise the patient's ability or desire to comply with treatment plans. If comorbid psychiatric conditions are present, they should be aggressively treated. The mental status of the patient should be evaluated; it should not be assumed that patients with cognitive impairments are unable to respond to pain-assessment questionnaires or provide an adequate self-report. The clinician may need to find alternative means of procuring necessary information in this patient population.

Multidisciplinary Assessment

Optimizing the treatment of patients with chronic pain or cancer pain often necessitates a multidisciplinary team approach. After careful assessment, the patient's complex pain complaint may require further assessment and treatment by specialists with pain expertise; such specialists include psychologists and psychiatrists, neurologists, anesthesiologists, physiatrists, pharmacists, physical/occupational therapists, vocational counselors, chaplains, and social workers. Pain clinics may be the best resource for such assessments and for team treatment; however, practitioners need to evaluate the pain clinics in their community to ensure that they provide a true multidisciplinary approach and not a monotherapeutic approach that principally utilizes nerve blocks and other invasive therapies.

Physical Examination

After procuring a complete and accurate patient medical history and self-report, it is critical to perform a detailed physical examination that includes a focused neurologic and musculoskeletal examination.[3] The physical examination can help determine the cause or causes of the pain and its relationship to an underlying disorder. Patients should be observed for compensating behaviors—so-called pain behaviors, such as exaggerated gait, distorted posture, and the guarding of areas. It is important to understand, however, that the absence of these behaviors does not indicate the absence of pain, nor does their presence indicate exaggeration, malingering, or a psychiatric condition. Patients often exhibit pain behaviors as a means of validating their pain. It is not uncommon for family members, employers, and health care providers to dismiss a person's pain in the absence of such behavior. Observation of the skin for the purpose of identi-

fying the presence of alterations in color, rash, erythema, and temperature changes may provide important evidence of dystrophic change with neuropathic pain.

Unrelieved chronic pain often accompanies neurologic disorders, sometimes in the absence of abnormal results on sensory examination. Focusing on symptoms can help clinicians avoid overlooking unrelieved pain during the course of the sensory examination. Sensory symptoms can be positive or negative as perceived by the patient. With negative symptoms, such as numbness, the patient's perception of a sign may decrease. For example, a patient may be less aware of mechanical stimulation, such as light touch, pinprick, warm, cold, or vibration. With positive sensory symptoms, the patient's perception increases; examples include mechanical or thermal allodynia (pain perception arising from a stimulus that is usually nonpainful, such as clothing, wind, heat, or cold), hyperalgia (an exaggerated response to a normally painful stimulus), and hyperpathia (an exaggerated response to a normally painful, often repetitive stimulus that occurs after an initial perception of less intensity). These conditions can exist with acute pain, but more commonly, they signal the existence of neuropathic pain processes.

Patients with neuropathic pain should be further evaluated to determine whether primary or secondary myofascial pain is present. Myofascial pain may be described by the patient in terms similar to those used to describe general neuropathic pain. It is a condition of abnormal muscle and soft tissue spasm and tightness that results in local and referred pain.[50] The musculoskeletal examination should include assessments of mechanical limitations of motion for the upper and lower extremities and the spine (cervical, thoracic, and lumbosacral). In the myofascial examination, the clinician uses palpation to search for evidence of soft tissue tightness and trigger points (i.e., focal areas of tightness and tenderness that reproduce pain and other symptoms upon palpation). The treatment approaches to myofascial pain and neuropathic pain differ; clinicians should therefore consider the distinct differences between myofascial and neuropathic pain processes when examining their patients.[50]

Diagnostic testing is usually unnecessary in determining the cause and magnitude of the pain complaint. Although it is important to review diagnostic studies such as MRI scans, radiographs, and computed tomographic scans in conjunction with physical findings to ensure that the appropriate anatomy has been imaged and to assess the relevance of any abnormal findings, accurate diagnoses are primarily based on medical history and physical examination. Moreover, it is critical to understand that an abnormality seen on neuroimaging or revealed by electrophysiologic testing need not convey any information about the site or the source of pain. For example, several studies have clearly demonstrated that abnormal findings on MRI do not correlate with back pain.[49] A recent large trial involving patients with rheumatoid arthritis found that abnormalities on x-rays weakly correlated with the patients' global pain assessments.[51]

In certain conditions, disease-specific laboratory parameters (e.g., the presence of tumor markers in cancer patients and $CD4^+$ T cell counts in AIDS patients) are sensitive indicators of disease progression and may be correlated with pain before other objective physical signs occur or radiographic signs become manifest.[3] It is helpful to make clinical inferences about the pathophysiologic mechanisms of pain, as these may guide diagnostic evaluations and even selection of analgesics or adjuvants for pain.

Follow-up

Routine patient reassessment completes the pain treatment cycle. Regular, ongoing reassessment is important in determining whether treatment goals are being met and allows for adjustments to be made to the plan to achieve optimal outcomes. Information solicited through reassessment should be documented in the patient's record to augment the clinician's understanding of the patient's pain problem and justify treatment decisions. The reassessment of patients after interventions, both pharmacologic and nonpharmacologic, can help determine the efficacy and tolerability of the treatment approach. (In deciding upon the timing of patient reassessment after pharmacologic interventions, consideration should be given to the pharmacokinetics of the medication and the need to titrate, taper, or add medication.) Reports of new pain must be investigated and a delineation made between progression of existing pain and development of new pain from a previously unknown source.

PAIN MANAGEMENT

Pain is a common occurrence in all clinical practices, being ever present in the entire spectrum of medical specialties—surgical and nonsurgical—and affecting all age groups. Anticipating and preventing pain and aggressively managing pain once it is present are critical to the promotion of healing, the alleviation of fear and anxiety, and the recovery of the nervous system to a state of normalcy.[52] If pain is left unchecked and untreated, the clinician will find pain more difficult to treat; in addition, the patient in pain will quickly develop secondary problems, including mood disturbances, insomnia, and problems arising from disuse.

Initial Analgesic Selection

The use of medications to provide pain relief is one of several options available to clinicians. Medications can be tremendous aids if used as part of a comprehensive plan to manage a patient's pain. Initial agent selection can be guided by information gleaned from a proper pain assessment and an understanding of the properties of available medications.[50] An understanding of the basic pathophysiology of pain and the pharmacology of medications can assist in the selection of medications that have a greater probability of success in treating the specific type of pain being encountered.[53] It is important that the clinician individualize the treatment plan for each patient's pain. The World Health Organization has published guidelines on the use of analgesics; these guidelines relate specific agents to the severity of pain and include adjuvant agents and nonopioid and opioid analgesics.[54]

Opioids, nonopioids, and adjuvant analgesics offer the clinician a plethora of pharmacotherapeutic choices. For the treatment of chronic pain and pain associated with cancer, it is not uncommon for patients to receive a combination of medications from each of these therapeutic classes; through this rational polypharmacy approach, optimal pain control is achieved through the utilization of medications with different mechanisms of action.

Patient Education

It is essential to include the patient in all treatment decisions from the beginning of treatment and to guide the patient toward a realistic expectation with regard to medication outcomes. Informing the patient of the expected onset of effect of medications, the duration of action, and side effects can enhance the pa-

tient's belief in the treatment plan. The patient who is aware of what to expect is better able to report on treatment efficacy and tolerability. It is critical that the patient have realistic expectations as to what degree of pain relief is most likely to be experienced with a specific treatment plan. A common impediment to the treatment of the patient with chronic pain is the patient's unrealistic expectation of complete pain relief through medications when only moderate or somewhat greater pain relief can realistically be expected.

When opioids are being prescribed, it is critical that the patient be educated about the differences between tolerance, physical dependence, and addiction [*see* Defining Addiction, Tolerance, and Physical Dependence, *below*]. All fears and misconceptions should be discussed openly, and questions should be answered honestly. The involvement of family members in such frank discussions can be a key factor in patient compliance and successful treatment. Preparing a patient to anticipate problems and to self-manage those problems restores a sense of control to the patient and can reduce the fear of and reluctance to use the medications prescribed.

Treatment Failure

Undertreatment in patients with pain often occurs when the dosages of opioids, nonopioids, and adjuvant analgesics are not optimized. Most often, this occurs through inadequate titration. Commonly, undertreatment of pain results from overly ambitious prescribing, whereby drugs are titrated too quickly or polypharmacy is initiated too soon. These actions result in intolerable side effects, causing the patient to become fearful of pain medications. Unfortunately, most clinicians are not properly trained as to the appropriate dosing of analgesics.

In certain patients with pain, physical and psychological treatments, often coupled with pharmacologic approaches, are as important as or even more important than pharmacologic therapies. These often successful therapies are outlined [*see Table 4*].

Analgesic Agents

OPIOID ANALGESICS

Indications

Opioids are most likely the oldest analgesic therapeutic class of drugs. They remain the cornerstone of therapy for the management of many pain conditions, including acute pain, postoperative pain, and cancer pain. In addition, over the past decade, randomized, controlled trials have demonstrated that some severe chronic-pain conditions can be successfully managed with opioid therapy; such conditions include osteoarthritis, low back pain, and neuropathic pain.[55-57]

Mechanism of Action

Opioids exert their effects through interaction with opioid receptors dispersed throughout the body. The CNS and gastrointestinal tract are the primary sites of these receptors.[58] Interestingly, over the past few years, it has become quite apparent that the opioids' analgesic activity is not solely the result of activity in the CNS; they are also active within the PNS, as demonstrated by the discovery of opioid receptors on peripheral nerves and soft tissues.[59]

Four types of opioid receptors have been identified: mu, kappa, delta, and sigma. These receptor types have been further subclassified into distinct subtypes.[58] Different opioids possess different affinity profiles for each opioid receptor type. This information may be of clinical value if it becomes necessary to switch opioids because of side effects. For example, in a patient experiencing dysphoria, the opioid may be switched to one with less sensitivity for either kappa or sigma receptors. In addition, opioids may vary with regard to other biologic effects that may affect a patient's response; a patient experiencing inadequate pain relief or intolerable side effects with one opioid may report significant pain relief without intolerable side effects with another opioid.[60] As an example, many opioids induce histamine release that may result in itching and worsening sedation, whereas others, such as oxymorphone, reportedly minimize this effect.[58]

Table 4 Pain-Management Modalities[3]

Modality	*Clinical Example for Use*	*Specific Example of Modality*
Pharmacologic	Complement to nonpharmacologic approaches; part of comprehensive pain-treatment plan	Opioids, nonopioids, topical agents, adjuvant agents, antineoplastic agents, radiopharmaceuticals
Nonpharmacologic		
Physical therapy	Complement to pharmacologic approaches addressing primary pain and secondary symptoms caused by disuse or inactivity	Superficial application of heat or cold, exercise, myofascial release, massage therapy, craniosacral manipulation, acupuncture, counterstimulation
Psychosocial	Address common comorbidities, depression, anxiety, and posttraumatic stress disorder; assist patient in sense of self-control and control of catastrophizing thoughts	Individual or group psychotherapy, relaxation, distraction, reframing, imagery, patient education, hypnosis, biofeedback
Radiation therapy	Complement to pharmacologic approaches for relief of metastatic cancer pain (i.e., refractory bone metastases)	Local radiation, radiopharmaceuticals
Anesthetic therapy	Pain confined to a specific area of nerves or spinal cord; reserved for instances in which pharmacotherapy, physical therapy, and radiation therapy are ineffective	Nerve blockade of specific plexus
Device implantation	Pain that is refractory to analgesics or anesthetic approaches	Spinal cord stimulation, implantable medication pump (opioids, clonidine, local anesthetics)
Neurosurgery	Pain that is refractory to analgesics or anesthetic approaches (should be utilized only in cancer pain)	Dorsal rhizotomy, myelotomy
Surgery	Reduction or excision of tumor	Lung cancer tumors causing spinal cord compression, nonmalignant tumors (e.g., neurofibroma) that directly impinge on nerve of viscera

Table 5 Equianalgesic Values[a] of Opioids[53,58,63,64,92]

Opioid	Equianalgesia		Type	Route of Administration[b]	Comments
	Parenteral	Oral			
Butorphanol	2 mg	N/A	Synthetic agonist-antagonist	I.V., I.M., nasal[c]	Dosing-ceiling effect; may precipitate withdrawal in opioid-dependent patients; antagonist activity one fortieth that of naloxone
Buprenorphine	0.3 mg	N/A	Semisynthetic partial agonist	I.M., I.V.	Dosing-ceiling effect; may precipitate withdrawal in opioid-dependent patients; antagonist activity equipotent to naloxone
Codeine	130 mg	200 mg[d]	Naturally occurring agonist	p.o., I.V., S.C., I.M.	Less potent than morphine; has strong antitussive effects
Fentanyl	0.1 mg	TD[e]	Synthetic agonist	T.D., T.M., I.V., I.M.	T.D. route not recommended for acute or unstable pain (delayed onset of action); opioid-naive patients should be titrated to starting dose of lowest T.D. strength
Hydrocodone	N/A	30 mg[d]	—	—	Available in multiple combinations with nonopioid analgesics
Hydromorphone	1.5 mg	7.5 mg	Semisynthetic agonist	p.o., P.R., S.C., I.V., I.M.	CR form under development; more potent than morphine
Levorphanol	2 mg	4 mg	Synthetic agonist	p.o., I.V., S.C., I.M.	High oral bioavailability; long biologic half-life after repeated administration
Meperidine	75 mg	300 mg	Synthetic agonist	p.o., I.M., S.C., I.V.	I.M. preferred route for repeated parenteral administrations; neurotoxic metabolite accumulation with repeated dosing limits multiple dosing
Methadone	10 mg	3–5 mg[f]	Synthetic agonist	p.o., I.M., S.C.	High oral bioavailability; short duration of effect, compared with long biologic half-life after repeated administration; difficult to switch to other agents
Morphine	10 mg	30–60 mg[g]	Naturally occurring agonist	p.o., P.R., S.C., I.V., I.M.	Standard for equianalgesia comparison; available in CR form; combination with NMDA receptor antagonist under investigation
Nalbuphine	10 mg	N/A	Synthetic agonist-antagonist	S.C., I.M., I.V.	Dosing-ceiling effect; may precipitate withdrawal in opioid-dependent patient; weak antagonist; psychomimetic effects possible but less than with pentazocine
Naloxone	—	—	Synthetic antagonist	I.V., I.M., S.C.	May induce withdrawal syndrome in opioid-dependent patient

Opioid Analgesic Subtypes

Opioids can be classified into three subgroups: agonists, antagonists, and agonist-antagonists. Agonists bind to and activate opioid receptors in asserting their pharmacologic analgesic effect. Agonists can be grouped according to the level of pain for which they are being used: moderate to severe pain or severe pain.

Opioid agonists for moderate to severe pain In clinical practice, opioids are commonly used in combination with acetaminophen, aspirin, and ibuprofen; examples of opioids used in such combinations are codeine, oxycodone, hydrocodone, and propoxyphene. These opioid and nonopioid agents used in combination provide analgesia through a dual mechanism of action, but they also have a dosing ceiling, which is determined by the amount of nonopioid analgesic (i.e., acetaminophen, aspirin, or ibuprofen) present in the formulation. The use of propoxyphene, whether as monotherapy or in combination, is limited by its long biologic half-life and the associated accumulation of its neurotoxic metabolite, norpropoxyphene. Norpropoxyphene is capable of producing CNS effects ranging from confusion to convulsions. For this reason, propoxyphene is not recommended as a first-line opioid for the treatment of moderate pain or for routine use in patients with cancer pain.[53]

Opioid agonists for severe pain Opioids that are effective for the treatment of acute and chronic severe pain include morphine, oxymorphone, oxycodone, hydromorphone, fentanyl, meperidine, and methadone [*see Table 5*]. Morphine is available in an injectable formulation, as an immediate-release tablet, as an extended-release tablet, in suppository form, as an oral solution, and as an oral concentrate. Morphine has a well-known

Table 5 (continued)

Opioid	Equianalgesia		Type	Route of Administration[b]	Comments
	Parenteral	Oral			
Naltrexone	—	—	Synthetic antagonist	p.o.	May induce withdrawal syndrome in opioid-dependent patient; greater oral bioavailability than with naloxone
Oxycodone	Not available in United States	20–30 mg	Semisynthetic agonist	p.o.	CR form available; initially 1.5 times more potent than morphine, but they become equipotent with repeated administration; many products combining oxycodone and nonopioid analgesics available
Oxymorphone	1 mg	10 mg	Semisynthetic agonist	P.R., S.C., I.V., I.M.	Oral CR and IR forms under development; more potent than oxycodone and morphine
Pentazocine	30 mg	50–200 mg	Synthetic agonist-antagonist	I.M., I.V., S.C.	Dosing-ceiling effect; may precipitate withdrawal in opioid-dependent patients; weak antagonist; psychomimetic effects possible
Propoxyphene	N/A	130 mg	Synthetic agonist	p.o.	Not more effective than APAP alone; neurotoxic metabolite
Tramadol	N/A	120 mg[h]	Central analgesic	p.o.	Dosing-ceiling effect; avoid in patients at risk for seizures; seizure risk increased in patients taking SSRIs, TCAs, or MAO inhibitors

[a]Equianalgesic value does not equal starting dose value. Starting dose value will depend on patient assessment and current opioid exposure.

[b]Does not include epidural, intrathecal, or intraventricular routes.

[c]Nasal dosage, 10 mg/ml; therapy is initiated as one spray (1 mg) in one nostril, repeated in 60–90 min. If relief is not adequate, dose is repeated in 3 to 4 hours p.r.n.

[d]Equianalgesic data unavailable.

[e]The dose of T.D. fentanyl, μg/hr, is one half the dose of p.o. morphine, mg/day (50 μg/hr patch q. 72 hr equals 100 mg/day of p.o. morphine).

[f]Many equianalgesic tables list 20 mg as the p.o. methadone equianalgesic dose; however, recent data suggest that methadone is more potent with repeated dosing. The ratio ranges from 1 mg of methadone to 4–14 mg of morphine.

[g]Single dose ratio is 6:1 p.o. to I.V./I.M./S.C., repeated dose ratio is 3:1 p.o. to I.V./I.M./S.C.

[h]Equipotent to 30 mg of morphine.

APAP—*N*-acetyl-*p*-aminophenol CR—controlled release I.M.—intramuscular IR—immediate release I.V.—intravenous MAO—monoamine oxidase N/A—not available NMDA—*N*-methyl-D-aspartate p.o.—oral P.R.—rectal S.C.—subcutaneous SSRI—selective serotonin reuptake inhibitor TCA—tricyclic antidepressant T.D.—transdermal T.M.—transmucosal

pharmacokinetic profile and is relatively inexpensive; thus, it is commonly considered the standard against which other opioid agonists are compared.[3,61,62] Oxymorphone is approximately 10 times more potent than I.V. morphine[63,64] and is currently available in an injectable form and as a suppository. Oxycodone is available as an immediate-release tablet, an extended-release tablet, and an oral concentrate solution. Oxycodone undergoes less first-pass hepatic metabolism and has higher bioavailability than morphine, yet it is equipotent to morphine, particularly after repeated administration.[64] Meperidine, which is most often administered by injection, is also available in an oral formulation. It has a short biologic half-life and is not available in a long-acting formulation. Normeperidine, a neurotoxic metabolite of meperidine, has a much longer biologic half-life than the parent compound and may accumulate, causing significant CNS adverse reactions, including agitation and even seizures.[53,58,62] Therefore, use of meperidine for more than a few days should be avoided. Many clinicians also recommend that meperidine not be used in patients with acute pain because of reports of seizures, even in patients who otherwise had normal renal function. Hydromorphone is currently available in injectable forms (including a highly concentrated formulation), as an oral liquid, as a rectal suppository, and as an immediate-release tablet; extended-release oral formulations are in development. Hydromorphone is more potent and more soluble than morphine, making the former particularly useful for patients who require a subcutaneous infusion at high doses. Fentanyl is currently available in a systemic transdermal patch, with a 48- to 72-hour clinical duration of effect. Clinical limitations with the fentanyl patch include the following: onset of effect is delayed; titration is challenging in patients with unstable or uncontrolled pain (i.e., pain that increases and decreases in intensity); and absorption of the drug can be affected by the patient's nutritional status and by concomitant diseases (e.g., peripheral vascular disease). Patients who are well nourished, whose skin is intact, whose pain is stable, and whose circulation is not compromised are most likely to have a favorable outcome. Fentanyl is also available in a formulation designed for oral transmucosal administration and in an intravenous formulation. Methadone is unfortunately not often considered an analgesic, in addition to its opioid properties, methadone is active at the NMDA receptor, making it a good opioid for the treatment of pain. Methadone lacks an active metabolite and has high oral bioavailability and rapid onset of analgesic effect; these characteristics, together with its low cost, make it an attractive opioid for use in cancer patients and patients with chronic pain. The fact that this agent has a relatively short therapeutic effect in relation to its long and varied biologic half-life (i.e., 15 to 40 hours) makes dosing a challenge. It is recommended that methadone be administered every 6 to 8 hours. A

second challenge with methadone involves switching to and from other opioid analgesics. Recent data have shown that when switching from methadone, the equianalgesic ratio may differ from that encountered when switching to methadone. In addition, some patients may respond only to methadone.[65]

Opioid antagonists The opioid antagonists naloxone and naltrexone bind to opioid receptors but do not exhibit any analgesic activity at currently available dosages. These agents are useful in treating opioid-associated respiratory depression, owing to the fact that they reverse the actions of opioid agonists. In addition, naloxone is useful in diagnosing physical dependence, and naltrexone is useful as an opioid detoxification adjunct [*see Table 5*]. An important characteristic of naloxone is that it has poor oral bioavailability, unlike naltrexone. The use of an opioid antagonist in patients receiving long-term opioid agonist therapy may result in a withdrawal syndrome and the return of excruciating pain.

Opioid partial agonists and mixed agonist-antagonists Partial agonists (i.e., agents that stimulate a particular receptor but that do not do so optimally) and agonist-antagonists (i.e., agents that stimulate one receptor subtype and block another) are generally inappropriate for the management of cancer pain or chronic pain because of their dosing ceiling, the fact that they precipitate opioid withdrawal in opioid-dependent patients, and the fact that they are associated with psychotomimetic effects, especially when taken with pentazocine.[58] Buprenorphine is a partial agonist; butorphanol, nalbuphine, dezocine, and pentazocine are agonist-antagonists [*see Table 5*]. Pentazocine is limited in its usefulness for mild to moderate pain, owing to its side-effect profile, and it is not recommended for use in patients with chronic cancer pain. Nalbuphine is useful in the management of acute pain. Intranasal butorphanol is often used for the treatment of postoperative pain and migraine pain. Buprenorphine is used for the treatment of moderate postoperative pain.[58] In general, the agonist-antagonists should be reserved for patients who are unable to tolerate a pure agonist.

Tramadol Tramadol does not fall into any of the previous three opioid classifications. It has moderate mu opioid receptor affinity and weak kappa and delta opioid receptor affinity. (The metabolite of tramadol binds more tightly than the parent; the mechanism underlying the level of analgesia that is achieved with tramadol is unknown.) Although tramadol is chemically unrelated to the opioid family, the side-effect profile of tramadol is similar to that of other opioids.[63,66] It also has weak serotonin and norepinephrine neurotransmitter reuptake inhibitory effects. Tramadol is used to treat moderate to moderately severe pain.[63] Tramadol lowers a patient's seizure threshold (i.e., makes a patient more vulnerable to seizures). This effect can be a problem when tramadol is administered with medications that can cause seizures, such as TCAs. Moreover, tramadol should not be used in patients who are at risk for seizures, such as patients with epilepsy and cancer patients with primary or metastatic brain tumors. The dosing ceiling of tramadol, as recommended by the manufacturer, is 400 mg a day. This dosing ceiling limits the usefulness of tramadol in the treatment of cancer pain or chronic pain. Furthermore, patient monitoring is important because seizures may occur in patients taking tramadol within the recommended dosing parameters[66] [*see Table 5*].

Defining Addiction, Tolerance, and Physical Dependence

Health care professionals and patients alike often lack an accurate understanding of drug tolerance, physical dependence, and addiction. Confusion about these conditions results in unfounded fears in both patient and physician regarding the use of opioids. This in turn leads to suboptimal use of opioids, particularly in the treatment of chronic-pain syndromes.[66] A number of professional organizations have worked to combat confusion and promote better understanding of the use of opioids. The American Society of Addiction Medicine (ASAM), the American Academy of Pain Medicine (AAPM), and the American Pain Society (APS) recently issued a consensus paper that defines addiction as a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations.[67] It is characterized by behaviors that include one or more of the following: impaired control over drug use; compulsive use; continued use despite harm, and craving. The degree to which a patient is at risk for addiction cannot be predicted. The use of opioids is only a contributing factor in some patients with predisposing characteristics.[68,69] In addition, the ASAM/AAPM/APS Consensus Group described a phenomenon known as pseudoaddiction. This condition occurs in a patient with pain who is not receiving optimal relief; the patient requests or ingests more medication than is prescribed, but these addictionlike behaviors abate when pain relief is achieved. It is important that clinicians properly distinguish pseudoaddiction from true addiction.[68]

Physical dependence and tolerance are pathophysiologic outcomes that should be expected in patients receiving long-term therapy with opioids; these effects should not be confused with addiction. Physical dependence is a state of adaptation that is manifested as a drug-class–specific withdrawal syndrome; physical dependence can occur as a result of abrupt cessation, rapid dose reduction, a decrease in the blood level of the drug, or administration of an antagonist.[68] Opioids are not the only drug class for which physical dependence commonly occurs; other frequently prescribed drugs that produce physical dependence include corticosteroids, beta blockers, and benzodiazepines. Discontinuance of these agents requires a slow tapering of therapy. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.[68]

Opioid Therapy

The decision as to which opioid to select should be dictated by a patient's individual need and should be guided by the drug's pharmacologic parameters. Key factors are as follows: (1) the drug's therapeutic half-life or duration of effect (i.e., long acting versus short acting); (2) onset of action (short-acting agents are desirable for breakthrough or incident pain); (3) route of administration (the oral route is less invasive); and (4) patient's experience with analgesics.[70]

Determining optimal dosage In general, one approach for opioid-naive patients is to administer immediate-release oral formulations for 24 to 48 hours as needed to relieve pain. Patients or caregivers should be encouraged to keep meticulous records to determine total medication consumption and response to therapy through use of a patient diary. This approach offers the clinician two advantages: an opportunity to determine the optimal amount of opioid necessary to manage

the patient's pain, and an opportunity to assist the patient in developing tolerance to some of the more common side effects.

Once an optimal amount of opioid has been determined, the opioid can be prescribed so as to provide relief around the clock through use of a long-acting formulation (e.g., sustained-release tablets). This is a standard practice for the management of cancer pain and chronic pain.[62] Even after the patient's opioid has been titrated to promote optimal pain relief and has been converted into a long-acting formulation, immediate-release agents should be available to the patient for use as rescue pain medication in the event of unexpected spikes in pain or an increase in pain as a result of activity or procedures (breakthrough or incident pain). The method of calculating the rescue dosage is described [*see* Opioid Conversion and Breakthrough Pain, *below*].

Side effects Opioids have well-described side-effect profiles. Sedation and nausea are common side effects that often occur at the onset of therapy but most often resolve after the first few days of treatment. Opioids directly stimulate the chemoreceptor trigger zone in the medulla, causing patients to develop nausea and vomiting. The use of antiemetic medications such as haloperidol or metoclopramide around the clock for the first 24 to 48 hours may alleviate any opioid-induced nausea and vomiting. Phenothiazines and antihistamines may be used to minimize nausea, but the anticholinergic side effects of these agents (e.g., dry mouth, urinary retention, sedation, constipation, dizziness, blurred vision, and tachycardia) may be particularly bothersome in the elderly. As the patient develops tolerance for the side effects, the antiemetic can be prescribed on an as-needed basis. In ambulatory patients, motion may contribute to the development or prolongation of nausea; scopolamine may be helpful in such patients.[62]

Another prevalent side effect of all opioids is constipation. Constipation is caused in part by the fact that the use of opioids leads to a decrease in intestinal secretions; an increase in electrolyte and water resorption from the large intestine; and a decrease in peristalsis, resulting in hard, dry stools.[58] If a patient who is receiving an opioid presents with abdominal pain or fullness, constipation or obstruction caused by the opioid should be considered in the diagnosis. A regimen directed toward preventing such bowel conditions should be initiated at the onset of opioid therapy in every patient; such a regimen should include a stimulant laxative and a stool softener, such as senna concentrate and docusate sodium.[62]

Sedation can be a problem at the onset of therapy or when it becomes necessary to increase the opioid dosage. For some patients, it is difficult to achieve a balance between adequate pain relief and tolerable levels of sedation. In treating patients with cancer pain, it is prudent to consider the use of stimulants, such as caffeine or methylphenidate.[71] In patients with chronic pain, the use of stimulants to offset opioid-induced sedation is not recommended.[72] Pain itself is a powerful stimulus, and it is important to bear in mind that sedation may result simply from the relief of pain itself, not as a side effect of opioid use. Patients may sleep more initially to catch up on the loss of rest caused by uncontrolled pain.

Respiratory depression is a feared, but extremely rare, adverse effect of the use of opioids. Although the danger is real, the occurrence of this problem is rare, particularly in patients who have received an opioid titrated to pain relief. Respiratory depression is caused by direct inhibition of the respiratory centers of the brain stem when the dose of an opioid is escalated too rapidly. Pain can counteract the depressant effects of opioids on the respiratory center, and therefore, the induction of rapid pain relief (i.e., removal of the stimulus) can contribute to respiratory compromise.[73] Patients with concomitant respiratory disease (e.g., chronic obstructive pulmonary disease) are at risk for respiratory depression.[74] Treatment of severe respiratory depression can be managed with naloxone (20 to 40 mg/min I.V.).[3,53] Withholding opioid use in a patient experiencing pain out of concern for respiratory depression is not a valid approach.

Other, less common side effects include myoclonus, hallucinations, and confusion; these effects may be caused by an accumulation of metabolites secondary to high-dose therapy, long-term therapy, renal dysfunction, or severe hepatic dysfunction. Approaches for the management of these effects include opioid rotation, reduction of dosage; the use of adjuvants that may permit a reduction in opioid dosage; and hydration (to increase renal elimination in patients who can tolerate excess fluid).[61] Clonazepam may be used to control myoclonic movements[53]; confusion may be treated with haloperidol.[62] Additional reported side effects include vertigo; sweating; hypotension and pruritus (secondary to histamine release); and urinary retention.[51]

Opioid conversion and breakthrough pain One of the most challenging and often least understood aspects of opioid therapy is conversion from one opioid analgesic to another. Change from one opioid to another may be necessitated by lack of efficacy or development of intolerable side effects. Clinicians often use published conversion tables to assist in the transition from one opioid to another.[3,63,64,75] The major problem occurs when a clinician fails to recognize the limitations of these conversion tables; these limitations arise from the fact that the data used to compute the tables are inadequate. Most conversion data were extrapolated from small, poorly designed trials. In many instances, a conversion parameter was not the primary efficacy variable of the study but was the result of a secondary observation. The use of conversion tables thus often leads to inappropriate opioid dosing; the dosages derived from conversion tables can be either higher or lower than the appropriate level. The issue of opioid conversion has risen in importance in recent years. The APS has established a panel to review all available source literature and to develop a new guideline for converting patients from one opioid to another; this guideline will be based on primary data from methodologically sound clinical studies.

Proper assessment is critical when one opioid analgesic is being switched to another. The severity of pain must be assessed when the initial dosage of the new opioid is being considered. Reassessment of pain serves to determine whether the pain currently experienced is a worsening of the original pain or a new type of pain (i.e., neuropathic pain); such new pain may be less responsive to opioids and may thus warrant the addition of the proper adjuvant (e.g., a TCA or an anticonvulsant). Sometimes, it is more prudent to add a medication from a different drug class than to switch to an alternative opioid.

Current equianalgesic conversion table data provide clinicians with a dosing starting point. There is no established right or wrong way to switch patients from one opioid analgesic to another. Perhaps the most important way for the clinician to become comfortable with switching opioids is to follow the same process each time. Suggestions for developing a consistent approach for conversion between opioid medications are presented [*see Table 6*].

A critical component of regimen redesign is the provision of an immediate-release opioid in the event the patient needs more relief during the first 24 to 48 hours after a change in regimen. The short-acting opioid breakthrough medication is an integral part of any long-acting opioid treatment plan for a patient with chronic pain or cancer pain. A short-acting opioid provides a means of dealing with acute episodes of pain that cannot be adequately controlled by the level of analgesia provided by the long-acting opioid. As with opioid conversions, there is no standard method for determining a breakthrough dose. Most clinicians use one of the following rules of thumb to calculate the milligrams per dose:

- 10% to 20% of the total daily dose[62,75]
- 25% to 30% of the single standing dose[62,75]

For example, a patient taking long-acting morphine at a dosage of 60 mg every 12 hours would have a breakthrough dose of either 15 to 25 mg (approximately 10% to 20% of total daily dose of 120 mg) or 20 to 30 mg (approximately 25% to 30% of the single dose of 60 mg). The duration of action of most short-acting opioids is 2 to 4 hours; therefore, the breakthrough regimens for the above example would be written as follows:

- 15 to 25 mg orally every 4 hours as needed for breakthrough pain
- 20 to 30 mg orally every 4 hours as needed for breakthrough pain

The initial dose of the new opioid will often need to be adjusted because of the changing needs of the patient and because the patient's level of tolerance of the new opioid may differ from that of the original opioid. The goal is to use the same opioid in both long-acting and short-acting forms so as to decrease the need for imprecise conversion ratios should titration be required.

Intravenous and subcutaneous administration Intravenous opioid administration may be useful for patients who are unable to use oral medications because of intractable nausea, concern for dysphagia or aspiration, or the need for high-dose therapy that would require the consumption of an unreasonable number of tablets or rapid titration to receive analgesic effect. Opioids are not subject to first-pass hepatic biodegradation; therefore, they have higher bioavailability through the intravenous route. Intravenous administration of opioids produces rapid onset of effect, although the duration of action is lessened after a single dose.[3] Continuous intravenous administration provides the patient with a consistent level of analgesia, and such administration can be easily achieved, particularly if central access has already been established. Subcutaneous administration can be employed when intravenous access is not readily available and when small fluid volumes can deliver the necessary amount of opioids. For both intravenous and subcutaneous administration, the risks of systemic side effects (e.g., respiratory depression) may be amplified, particularly if the patient is opioid naive or if significant dose escalation occurs over a short period of time. Intramuscular administration should be avoided when possible because of erratic absorption and intense pain associated with drug deposition into muscle. Otherwise, with prudent titration and monitoring of the patient, the side-effect profiles of opioids are manageable.

Intraspinal opioid administration In some patients who require large amounts of opioid, adequate drug levels cannot be achieved because of systemic side effects. Such patients are candidates for the administration of opioids into the epidural or intrathecal space. By confining opioid exposure to the large concentration of opioid receptors residing in the area of the spinal cord dorsal horn, analgesia is achieved with a smaller amount of opioid. Generally, intrathecal morphine is 10 times more potent than epidural morphine, which is 10 times more potent than intravenous morphine.[75] As with many acceptable approaches to pain management, intraspinal opioid administration has been examined primarily for cancer pain treatment. However, attention is being given to the efficacy of this approach in the treatment of selected patients with chronic pain who do not have cancer, and this approach is being used more in such patients.[76,77] Importantly, intraspinal administration is not a first-line treatment. Intraspinal administration of opioids should be considered only in patients in whom all other conservative therapies have failed and in patients who have experienced partial pain relief with multiple trials of several oral or transdermal opioids but who have experienced intolerable side effects with each.

Adjunct medications such as local anesthetics and clonidine have been used with opioids to manage intractable cancer pain or neuropathic pain.[78] In randomized, controlled trials, intrathe-

Table 6 Recommended Steps in Converting a Patient's Regimen from One Opioid to Another

1. Globally reassess the patient [*see Table 3*] to determine whether the increase in pain is secondary to worsening of existing pain or development of a new type of pain.
   - If there are inflammatory or neuropathic components to the pain, consider the addition of an adjuvant (with specified mechanism of action targeting the suspected nature of the pain) instead of continued titration of the same opioid or switching to another opioid.
   - If the patient is receiving an opioid, consider untreated or undertreated constipation as a potential source of the pain.

   The next three steps are based on the assumption that the pain is responsive to opioids and that the current opioid has been titrated to maximal effect and the patient is either still in pain or experiencing intolerable side effects, and thus a switch to an alternate opioid is warranted.
2. Determine the total daily usage of the current opioid. This should include all long-acting and breakthrough opioid doses.
   - If the patient is receiving multiple opioids, convert all to morphine equivalents. The goal is to reduce all medication usage to one common denominator.
3. Decide which opioid analgesic will be used as the new agent, and consult established conversion tables to arrive at the proper dose of the new opioid, recognizing the limitations of the data.
4. Individualize the dosage on the basis of assessment information gathered in step 1 and ensure adequate access to breakthrough medication. It is suggested to then reduce the calculated dose by 25% to 33%, owing to lack of cross-tolerance between agents. This is a good approach to use when changing opioids becomes necessary as a result of intolerable side effects in patients with adequate pain control. A moderate or more aggressive regimen may be selected for patients who report severe pain and whose pain substantially interferes with their quality of life. The ultimate decision of whether to be conservative or aggressive is based on preference, experience, comfort with the process of opioid conversion, the patient's ability to tolerate the drug, and the patient's trust of the clinician.
5. Continually reassess the patient, especially during the first 7 to 14 days, for the total daily dose (extended release + immediate release) and increase or decrease the around-the-clock extended-release dosage accordingly.

cal clonidine was shown to be of benefit for patients with refractory neuropathic pain[76,79], it has not been approved by the Food and Drug Administration for the treatment of severe pain when used in combination with opioids in cancer patients whose pain is not relieved by opioid analgesics alone.[63]

NONOPIOID ANALGESICS

Nonopioid broad-spectrum analgesics include NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, acetaminophen, and salicylates. These drugs are most often used as the sole treatment for mild to moderate acute and chronic pain; they are also often used as part of comprehensive, polypharmacy drug-treatment regimens for the alleviation of difficult and refractory chronic-pain conditions.

NSAIDs is a loosely used term denoting a varied group of agents exerting antipyretic, analgesic, and anti-inflammatory effects. (It is important to note that acetaminophen exerts analgesic and antipyretic effects; it does not possess anti-inflammatory properties.) These agents can be categorized into nonspecific COX inhibitors (e.g., aspirin, acetaminophen, ibuprofen, and naproxen) and COX-2 selective inhibitors (e.g., celecoxib and rofecoxib). Cyclooxygenase is necessary for the conversion of arachidonic acid into prostaglandins, prostacyclin, and thromboxane. These end products of the arachidonic acid pathway mediate a large number of bodily processes, including pain and inflammation, secretion of a protective gastric layer, maintenance of renal perfusion, and platelet aggregation. NSAIDs block the action of cyclooxygenase, thereby reducing the production of these mediators. This results in both positive and negative physiologic effects. Positive effects include reduced pain and inflammation; negative effects include gastric ulceration, bleeding, and decreased renal perfusion. It is important to realize that the anti-inflammatory potency of these drugs is not correlated with their analgesic potency; that is, an NSAID that demonstrates superior anti-inflammatory effects is not necessarily a potent analgesic.[80] Moreover, there is growing evidence that the analgesic mechanism of action of at least some NSAIDs and COX-2 inhibitors lies in the CNS.[81]

COX-1 is found primarily in the renal parenchyma, the gastric mucosa, and other tissues and in platelets. It helps maintain normal function. COX-2 is found in large quantities at sites of inflammation and contributes to the inflammatory response mediated by prostaglandins. COX-2 does not play a protective role in the cells and tissues in which it is found. NSAIDs nonselectively inhibit both COX-1 and COX-2. On the other hand, COX-2 inhibitors selectively target the enzyme involved in the production of the prostaglandins responsible for mediating the transduction of pain signals and inflammation, but it does not interfere with the prostaglandin production associated with gastric mucosal protection, renal blood flow, and platelet coagulation.[82,83]

Most studies have shown that the analgesic efficacy of the COX-2 inhibitors is not superior to that of the NSAIDs. Although the COX-2 inhibitors have been touted as having better side-effect profiles than the NSAIDs, the clinical relevance of this to the population at large has been questioned.[84] Recent reviews have called for trials to specifically characterize cardiovascular and renal effects of these agents.[85,86] Therefore, although the currently available COX-2 inhibitors are widely prescribed and have become first-line agents for many physicians, the risk-to-benefit data may not support their use as first-line agents unless the patient is at high risk for adverse events (e.g., the patient has a history of GI bleeding).

In selecting a nonopioid analgesic, the clinician should take into account the patient's age, concomitant disease states, and the risk of side effects. As a class of medications, NSAIDs can directly and indirectly assault the gastric mucosa because of the weak acidity of NSAIDs; this in turn causes local irritation and the inhibition of protective prostaglandins. Because NSAIDs decrease renal perfusion, patients whose renal blood flow is compromised (e.g., patients receiving concomitant diuretic therapy, patients experiencing dehydration, and those with long-standing cardiac disease) may be at risk for acute renal failure. Patients at risk for bleeding (e.g., patients receiving anticoagulation therapy) must be monitored when using NSAIDs that have a greater potential to affect platelets, particularly aspirin, which has irreversible effects on platelets. Choline magnesium trisalicylate may be an alternative, because it causes less irritation to the gastric mucosa and does not demonstrate significant effects on platelets. COX-2 inhibitors were designed to avoid the major side effects of the NSAIDs through their selectivity, but the actual clinical data and their implications are unclear (see above). The currently available nonopioid agents and their recommended adult dosages are listed [*see Table 7*].

All NSAIDs and COX-2 inhibitors have dosing ceilings; surpassing these dosing ceilings puts the patient at greater risk of toxicity without increasing efficacy. Acetaminophen is worthy of particular mention because it can be found in numerous over-the-counter (OTC) and prescription preparations. In healthy adults, serious hepatic toxicity can occur when dosages of acetaminophen exceed 4 g/day. Potentially fatal hepatotoxicity can occur at lower daily dosages of acetaminophen in patients who abuse alcohol. Thus, patients must be encouraged not to take excessive amounts of acetaminophen. Patients should also be encouraged to pay attention to the contents of all OTC combination products and to inform their physician or pharmacist if they are using a product containing acetaminophen when a prescription for an analgesic is written or filled.

ADJUVANT ANALGESICS

By definition, adjuvant analgesics are medications that have been demonstrated to have analgesic properties but that have not been approved by the FDA for the treatment of pain. In fact, many, if not most, of the drugs currently prescribed to treat some chronic-pain conditions (e.g., neuropathic pain, fibromyalgia, and even chronic headache) have not been approved by the FDA for such use (i.e., the drugs are employed in so-called off-label use). There are two likely reasons for this: (1) many of these agents were found to possess analgesic properties after the drug had become a generic product and, thus, no pharmaceutical company would invest the millions of dollars needed to obtain FDA approval (an example of such a drug is amitriptyline), and (2) the pharmaceutical industry ignored the chronic-pain market because it was believed that there was no need for such drugs and that the market was too small. Over the past several years, the need for product research and development has been recognized. A remarkable number of new drugs, as well as drugs approved for other indications, are being evaluated for the treatment of pain. Thus, it may be that the term adjuvant analgesic will eventually fall out of use. The most commonly prescribed adjuvant analgesics are the following: antidepressants, anticonvulsants, local anesthetic antiarrhythmics, corticosteroids, and sympatholytic agents. Antidepressants and anticonvulsants are discussed (see below), and the remaining categories are outlined [*see Table 8*].

Table 7 Nonopioid Analgesics[62,63,114]

Generic Name	*Brand Name*	*Usual Adult Dosing Range*[a]	*Maximum Recommended Dose*
Acetaminophen	Tylenol, Feverall, various	325–650 mg q. 4–6 hr	4 g/day
Aspirin	Bayer, Empirin, various	325–650 mg q. 4 hr	4 g/day
Celecoxib	Celebrex	100 mg q. 12 hr or 200 mg q.d.	200 mg/day
Choline magnesium trisalicylate	Trilisate, various	500 mg to 1,500 mg p.o., q. 8–12 hr	4.5 g/day
Diclofenac potassium	Cataflam, various	50 mg q. 8 hr or 75 mg q. 12 hr	150 mg/day
Diclofenac sodium[b]	Voltaren, various	50 mg q. 8 hr or 75 mg q. 12 hr[c]	150 mg/day
Diflunisal	Dolobid, various	250–500 mg q. 8–12 hr	1.5 g/day
Etodoloc	Lodine, various	200–400 mg q. 6–8 hr	1.2 g/day
Etodoloc extended release[d]	Lodine XL	400–1,000 mg q. 24 hr	1.2 g/day
Fenoprofen	Nalfon, various	200 mg q. 4–6 hr	3.2 g/day
Flurbiprofen	Ansaid, various	200–300 mg/day in two to four divided doses	300 mg/day
Ibuprofen	Motrin, various	200–400 mg q. 4 hr	3.2 g/day
Indomethacin[b]	Indocin, various	75–150 mg in three or four divided doses	200 mg/day
Ketoprofen	Orudis, various	25–50 mg q. 6–8 hr[e]	300 mg/day
Ketoprofen extended release[d]	Oruvail	100–200 mg q.d.	200 mg/day
Ketorolac[f]	Toradol, various	10 mg q. 4–6 hr	40 mg/day x 5 days
Meclofenamate	Various	50 mg q. 4–6 hr	400 mg/day
Mefenamic acid	Ponstel	250 mg q. 6 hr	1 g/day; not to exceed 1 wk[g]
Nabumetone	Relafen	500 mg b.i.d. or 1,000 to 2,000 mg q.d.	2 g/day
Naproxen	Naprosyn, various	250–500 mg q. 8–12 hr	1.25 g/day
Naproxen controlled release[d]	Naprelan	750–1,000 mg q. 24 hr	1.5 g/day[h]
Naproxen delayed release[d]	EC-Naprosyn, various	375–500 mg q. 12 hr	1 g/day
Naproxen sodium	Anaprox, various	275–550 mg q. 6-12 hr[e]	1.375 g/day
Oxaprozin	Daypro	600–1,200 mg q. 24 hr	1.8 g/day
Piroxicam	Feldene	10 mg q. 12 hr or 20 mg q. 24 hr	20 mg/day
Rofecoxib	Vioxx	12.5–25 mg q. 24 hr[i]	25 mg/day
Sulindac	Clinoril, various	150–200 mg q. 12 hr	400 mg/day

[a]Recommendations do not consider impaired organ function. Refer to alternative reference for dosing adjustment recommendations.
[b]Available in extended-release and delayed-release forms; these forms are not described in this table.
[c]Up to 200 mg may be used in the initial 24 hrs.
[d]Tablets are not to be broken, crushed, or chewed.
[e]Dosage for prescription version.
[f]Ketorolac is available in injectable form. The usual adult dosing recommendation is 15–30 mg I.V. or I.M. q. 6 hr for a maximum of 5 days.
[g]On the first day of dosing, 1,250 mg may be used.
[h]For limited time dosing.
[i]Doses of 50 mg q.d. for up to 5 days may be used to treat pain; no studies have tested the use of this dose for longer periods.

Antidepressants

TCAs have been used for many years to treat chronic-pain conditions. Much indisputable evidence from both human and animal studies demonstrates that the TCAs have analgesic effects independent of their effect on mood.[87] Many controlled trials involving patients with postherpetic neuralgia[88] and painful peripheral diabetic neuropathy[37,89] have clearly demonstrated the efficacy of several TCAs. Some authorities have suggested that two types of TCAs are superior: (1) those that inhibit the reuptake of both norepinephrine and serotonin and (2) those that selectively inhibit the reuptake of norepinephrine, rather than serotonin.[90] Meta-analysis and literature review articles have reported the analgesic efficacy of tricyclic antidepressants.[87,91]

The newer selective serotonin reuptake inhibitors (SSRIs) have not been found to have significant analgesic activity.[87,92] Most controlled trials have reported negative results[37,93] or marginal efficacy with paroxetine.[94,95] Thus, SSRIs are not recommended for use as analgesics in patients with neuropathic pain.

Classically, the analgesic effects of the TCAs were thought to be the result of the action of these agents on serotonin and norepinephrine in the pain-modulating system—a series of neuronal networks starting in the brain stem and synapsing in the dorsal horn. However, this hypothesis has little convincing support. Studies of peripheral neuropathic pain in animal models suggest that the analgesic effects of these agents are achieved through their blocking of the sodium channel[96]; this hypothesis is indirectly supported by the fact that the TCAs have local anesthetic pharmacologic activity.

Amitriptyline is the prototypical TCA and the most widely studied TCA for the treatment of pain. Among TCAs, amitriptyline also has the greatest potential for causing dose-limiting side effects. The TCAs nortriptyline, desipramine, and imipramine have been shown to be efficacious in controlled trials and to have fewer side effects than amitriptyline.[90] Regardless of the TCA chosen, it is prudent to start with a low dose of 25 mg a day at night for adult patients to minimize the development of anticholinergic side effects. In elderly patients, the initial dose should be 10 mg a day, given at bedtime. Elderly patients tend to be more susceptible to the anticholinergic side effects (see below). The dose needs to be gradually increased weekly until the patient reports satisfactory pain relief or intolerable side effects. The effective dose varies among patients, ranging from 10 to 150 mg a day; the typical dose is from 25 to 75 mg. Patients experience the analgesic effects of TCAs within 1 to 2 weeks of achieving their therapeutic dose. Serum levels of drug do not correlate to response; hence, it is not necessary to follow serum levels.

A common side-effect profile for all TCAs includes weight gain, sedation, and orthostatic hypotension. However, TCAs are often used specifically for their sedating effects as a treat-

ment of insomnia, a common comorbid condition in patients with chronic pain. Anticholinergic side effects include dry mouth, blurred vision, constipation, and urinary retention. Patients at risk for seizures or those with cardiac dysfunction (e.g., arrhythmias or heart failure) are not good candidates for amitriptyline, because a patient's seizure threshold may be reduced or cardiotoxicity may occur. Cardiotoxicity rarely occurs if cardiac function is normal.

Venlafaxine Venlafaxine inhibits the reuptake of both serotonin and norepinephrine, but unlike the TCAs, it does not have clinically meaningful effects on the cholinergic systems or histamine. It reportedly has fewer side effects because it does not bind to those receptor sites responsible for common side effects induced by the TCAs. Case reports have shown venlafaxine to be effective, and randomized, controlled trials with healthy persons have shown promise[97]; however, further studies are needed.

Anticonvulsants

The use of anticonvulsants for the treatment of various types of neuropathic pain is well documented. Although the exact mechanism of action of anticonvulsants in neuropathic pain is uncertain, common pathophysiologic and biochemical mechanisms have been observed in both neuropathic pain and epilepsy.[98] The most likely mechanism for many of the analgesic properties of the anticonvulsants, at least in the treatment of neuropathic pain, is sodium channel blockade. Activation of NMDA receptors has been implicated in both kindling of hippocampal neurons in epilepsy and windup (central sensitization) in neuropathic pain.[98] The mechanism of action of both the epileptic and the analgesic activity of gabapentin, which is currently the anticonvulsant that is most prescribed for pain, is still unknown.

The use of anticonvulsants in neuropathic pain syndromes (e.g., trigeminal neuralgia, diabetic neuropathy, and postherpetic neuralgia) dates back to 1942.[99] Poor design of the earlier anticonvulsant trials involving phenytoin and carbamazepine makes clinical interpretation difficult. Early trials have been criticized for the omission of drug-dosage information, the lack of true blinding, inappropriate statistical conclusions, and the omission of statistical testing.[91]

Gabapentin Gabapentin has become a first-line treatment of most neuropathic pain conditions, primarily on the basis of its superior side-effect profile, as compared with other systemic agents, and the results of randomized, controlled trials. Two recently published, well-designed clinical trials have established its effectiveness in both diabetic neuropathy and postherpetic neuralgia.[100,101] In 1998, Backonja and colleagues published the results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 165 patients with a 1- to 5-year history of pain attributed to diabetic neuropathy. The dose of gabapentin was titrated from 900 mg/day to 3,600 mg/day; pain relief was noted by the investigators 2 weeks after the dose reached 1,800 mg/day. Mean daily pain scores in the gabapentin group (baseline, 6.4; end point, 3.9) were significantly lower ($P < 0.001$) than those in the placebo group (baseline, 6.5; end point, 5.1). Sixty percent of the gabapentin group reported moderate or greater pain relief, compared with 33% of those receiving placebo. Results of the Medical Outcomes Study 36-Item Short Form (SF-36) and the Profile of Mood States (POMS) showed significant differences favoring gabapentin. Dizziness and somnolence were the two most reported adverse effects in the gabapentin group.[100]

A multicenter, randomized, double-blind, placebo-controlled, parallel-design study conducted in 1998 evaluated the efficacy and safety of gabapentin in patients with postherpetic neuralgia pain. In this 8-week trial, a total of 229 patients were randomized to receive either gabapentin or placebo. During a 4-week titration phase, patients were titrated to a maximum dose of 3,600 mg/day or the maximum tolerable dose. Treatment was maintained for 4 weeks at the maximum tolerated dose. The primary efficacy measure was change in pain from baseline to the final week of therapy. The degree of pain was assessed through use of the 11-point Likert scale, in which 0 indicates no pain and 10 indicates the worst possible pain. Gabapentin demonstrated analgesia superior to that of placebo. In the gabapentin group, the patients' average daily pain score was reduced from 6.3 to 4.2; for the patients receiving placebo, the pain score moved from 6.5 to 6.0 ($P < 0.001$). In addition, 43.2% of those who received gabapentin reported at least moderate pain relief, compared with 12.1% of the placebo group. The most common adverse effects in the gabapentin group were somnolence, dizziness, ataxia, peripheral edema, and infection. Withdrawal rates in the gabapentin and placebo groups were comparable.[101]

Other trials have shown gabapentin to be efficacious as an adjunct to opioid analgesia in the treatment of neuropathic cancer pain.[102] In a comparison study, gabapentin demonstrated a degree of efficacy similar to that of amitriptyline in patients with diabetic peripheral neuropathy.[89] A small study of 18 patients published in 1999 reported a lack of convincing evidence for gabapentin in the treatment of patients with upper extremity type 1 complex regional pain syndrome (CRPS).[103]

Gabapentin is currently the first-line systemic agent for the treatment of neuropathic pain, on the basis of published clinical trials, large and growing clinical experience, its lack of drug-drug interactions, and its side-effect profile. It should be noted, however, that a significant number of patients report intolerable or bothersome side effects with gabapentin, including sedation, dizziness, and peripheral edema. The current recommended dosing guidelines are as follows: an initial dose of 300 mg at bedtime, followed by an increase in dosage to 300 mg twice a day and then three times a day every 5 to 7 days as needed. Some patients with pain prefer a dosage of four times a day. If a patient is not experiencing any significant pain relief or side effects, the dose can be increased by 300 mg every 7 days until significant relief or side effects occur. Because some patients may require up to 6,000 mg before experiencing adequate pain relief, a potential clinical problem with gabapentin is the long period needed to reach a therapeutic dose (this period can be 1 to 2 months). Thus, close and regular patient follow-up and monitoring are recommended while the optimal dose is being titrated.

Carbamazepine Carbamazepine was the first agent to receive FDA approval for treatment of a specific type of neuropathic pain—trigeminal neuralgia. This approval and the subsequent clinical benefits for patients with such pain led clinicians to test carbamazepine for other types of neuropathic pain, including diabetic neuropathy, postherpetic neuralgia, and central pain syndromes.[98]

In a crossover study in 70 patients with trigeminal neuralgia, patients receiving carbamazepine (400 to 800 mg/day) experienced a 58% improvement; this compared with a 26% improvement in patients who received placebo.[104] In a small crossover

Table 8 Adjuvant Agents Primarily Used to Address Neuropathic Pain[70,86,114]

Generic Name	*Brand Name*	*Mechanism of Action*	*Usual Adult Starting Doses*	*Titration*
Carbamazepine*	Tegretol, various	Sodium channel blockade	100 mg b.i.d.	100 mg q. 3–7 days
Gabapentin	Neurontin	Effect on α-2-δ Ca^{2+} channels	300 mg q h.s	300 mg q. 3–7 days
Lidocaine patch 5%*	Lidoderm	Blocks peripheral sodium channels located in damaged/dysfunctional nerves and provides mechanical protection of allodynic skin	1 to 3 patches applied directly to painful area; on 12 hr/off 12 hr	None required
Mexiletine	Mexitil	Sodium channel blockade	150 mg q.d.	150–200 mg q. 3–7 days in divided doses
Phenytoin	Dilantin, various	Sodium channel blockade	100 mg b.i.d.	Titrate to relief or intolerable side effects
Tizanidine	Zanaflex	Central muscle relaxation via alpha-adrenergic agonist	2 mg q.h.s.	2 mg every 3 to 7 days in divided doses
Nortriptyline†	Pamelor, various	Neurotransmitter reuptake inhibitor	10–25 mg q.h.s.	Titrate to response or intolerable side effects
Desipramine†	Norpramine, various	Neurotransmitter reuptake inhibitor	10–25 mg q.h.s.	Titrate to response or intolerable side effects
Amitriptyline†	Elavil, various	Neurotransmitter reuptake inhibitor	10–25 mg q.h.s.	Titrate to response or intolerable side effects
Doxepin†	Sinequan, various	Neurotransmitter reuptake inhibitor	10–25 mg q h.s.	Titrate to response or intolerable side effects
Corticosteroids	Various	Anti-inflammatory effects; sodium channel blockade; reduces capillary permeability	Pulse therapy recommended for early CRPS only	Long-term use not recommended
Clonidine	Catapres (p.o.), various; Duraclon (I.V.)	Partial alpha-adrenergic blockade	0.1 mg b.i.d. or transdermal therapeutic system (TTS-1)	Titrate to relief or intolerable side effects
Baclofen	Lioresal, various	Mechanism of action unknown; GABA analogue, central muscle spasticity	5 mg t.i.d.	15 mg every 3 days

study involving 30 patients, those receiving carbamazepine experienced a 70% improvement, compared with minimal or no improvement in the patients who received placebo.[105] Similar results were reported in a partial crossover study; in this study, patients who received carbamazepine experienced a 75% improvement, compared with a 25% improvement in patients who received placebo.[106] However, limitations in study methodology make it difficult to fully assess the evidence from these trials.

Several double-blind trials comparing carbamazepine with other active agents in patients with diabetic neuropathy showed mixed results. The dosage for carbamazepine ranged from 300 to 2,400 mg/day, administered in divided doses. The most common side effects reported with carbamazepine are dizziness and somnolence. Patients receiving long-term carbamazepine therapy should be monitored for abnormal liver function; in addition, patients should be monitored for GI disturbances and, rarely,

Table 8 (continued)

Maximum Dose	Expected Side Effects	Contraindications	Additional Comments
Titrate to relief or intolerable side effects	Ataxia, confusion, nausea, liver toxicity, blood dyscrasias, Stevens-Johnson syndrome	Liver abnormalities, bone marrow suppression, known sensitivity to tricyclic antidepressants	Approved by FDA for trigeminal neuralgia
6,000 mg/day (q.i.d. dosing)	Sedation, dizziness, fatigue, confusion, weight gain	Known sensitivity to drug or its ingredients	—
3 patches	Mild and transient skin irritation at application site	Known sensitivity to amide local anesthetics	Lidocaine levels are 1/10 the antiarrhythmic treatment dose; only FDA-approved treatment for postherpetic neuralgia
1,200 mg/day (recommended to obtain serum level at 900 mg/day)	Nausea, vomiting, dizziness, tremor at higher doses; seizures possible at excessive doses	Second- or third-degree heart block	Take with food, if possible; avoid administration within 1 hr of taking antacids
100 mg q. 3–7 days	Sedation, nausea, ataxia, dizziness, confusion, gingival hyperplasia, nystagmus, blood dyscrasias, Stevens-Johnson syndrome	Known hypersensitivity, sinus bradycardia, sinus arrhythmia block, second- or third-degree heart block	Losing favor as newer agents become available; take with food to minimize GI effects
36 mg/day	Sedation, hypotension, dizziness, liver function abnormalities (monitor initially), dry mouth	Hypersensitivity to drug or its ingredients	Liver function monitoring recommended at 1, 3, and 6 mo after initiation
150 mg/day	Sedation, orthostatic hypotension, weight gain, anticholinergic effects (dry mouth, constipation, urinary retention); lower seizure threshold (caution in patients at risk for seizures)	Known hypersensitivity; concurrent administration of an MAO inhibitor, second- or third-degree heart block, arrhythmias	Less anticholinergic side effects than with amitriptyline
150 mg/day	Sedation, orthostatic hypotension, weight gain, anticholinergic effects (dry mouth, constipation, urinary retention); lower seizure threshold (caution in patients at risk for seizures)	Known hypersensitivity; concurrent administration of an MAO inhibitor, second- or third-degree heart block, arrhythmias	Less anticholinergic side effects than with amitriptyline; less sedation
150 mg/day	Sedation, orthostatic hypotension, weight gain, anticholinergic effects (dry mouth, constipation, urinary retention); lower seizure threshold (caution in patients at risk for seizures)	Known hypersensitivity; concurrent administration of an MAO inhibitor, second- or third-degree heart block, arrhythmias	Greatest anticholinergic side effects; hard candy may help with dry mouth
150 mg/day	Sedation, orthostatic hypotension, weight gain, anticholinergic effects (dry mouth, constipation, urinary retention); lower seizure threshold (caution in patients at risk for seizures)	Known hypersensitivity; concurrent administration of an MAO inhibitor, second- or third-degree block, arrhythmias, glaucoma; patients with tendency for urinary retention	High degree of sedation
Long-term use not recommended	Short term: hypertension, hyperglycemia, immunosuppression, cognitive impairment	Known hypersensitivity to drug or systemic fungal infections	Dexamethasone causes less sodium and water retention; not generally recommended for neuropathic pain treatment
2.4 mg/day	Dizziness, drowsiness, sedation, weakness, hypotension, constipation, dry mouth, itching; use with caution in patients with severe coronary disease	Known hypersensitivity to drug; any component of the adhesive layer of the transdermal system	Do not discontinue abruptly; I.V. clonidine indicated for severe pain that is unrelieved by opioids alone as an add-on agent
80 mg/day	Nausea, drowsiness, dizziness	Elderly patients may be sensitive to side effects	Rapid discontinuance can lead to delirium or seizures

*Only carbamazepine and the lidocaine 5% patch have been approved by the Food and Drug Administration (FDA) for treatment of a type of neuropathic pain; carbamazepine is indicated for trigeminal neuralgia, and the lidocaine 5% patch is indicated for postherpetic neuralgia.
†Tricyclic antidepressant.
CRPS—complex regional pain syndrome GABA—γ-aminobutyric acid MAO—monoamine oxidase TCA—tricyclic antidepressant

hematopoietic complications, such as aplastic anemia. Carbamazepine is an enzyme inducer and can accelerate the metabolism of other medications, thereby reducing their therapeutic effect, as is the case with theophylline.

It is currently recommended that carbamazepine be a first-line treatment of trigeminal neuralgia but not for any other neuropathic pain condition. Clinical experience indicates that its efficacy in nontrigeminal neuralgia pain is marginal; in addition, many patients experience intolerable side effects. For the symptomatic treatment of pain associated with trigeminal neuralgia, the usual initial adult dosage of carbamazepine is 100 mg twice daily. The dosage may be increased gradually by up to 200 mg

daily in 100 mg increments every 12 hours until pain relief is achieved. Carbamazepine has the ability to induce its own metabolism, particularly at the initiation of therapy or when titration occurs too rapidly. The consequences of autoinduction are an increase in the rate of metabolism, an enhancement of oral first-pass effect, and a decrease in bioavailability (the decrease in bioavailability reflects a decrease in blood plasma concentration).[107] After pain control is achieved, maintenance dosages of 400 to 800 mg daily are usually adequate; however, some patients may require as little as 200 mg daily, whereas others may require 1.2 g daily.[108]

Phenytoin As with studies of carbamazepine, the published trials of the use of phenytoin in patients with pain associated with nontrigeminal neuralgia are weakened by the small size of the trials and suboptimal methodology. The results have been conflicting. Most clinicians no longer view phenytoin as a first-line agent for the treatment of neuropathic pain. Phenytoin remains a preferred treatment only for trigeminal neuralgia.

Valproic acid In a a small, double-blind, placebo-controlled study, valproic acid was given to patients with severe chronic central pain associated with spinal cord injury. No significant analgesic effects of valproic acid were demonstrated, despite the fact that the serum concentration and dose of valproic acid reached high levels.[109] Valproic acid is not currently recommended as a treatment for pain other than migraine.

Lamotrigine Lamotrigine is a new-generation antiepileptic drug that has sodium channel–blocking activity and that inhibits the release of glutamate.[110,111] In a number of clinical trials, lamotrigine has been shown to be effective in the treatment of trigeminal neuralgia,[112-114] HIV-associated polyneuropathy,[115] diabetic neuropathy,[116] and other neuropathic pain syndromes. However, in a recent trial in patients with neuropathic pain, no benefit was shown with the use of lamotrigine.[110] The patients in this trial were diagnosed as having neuropathic pain on the basis of the presence of at least three cardinal symptoms, which included shooting or lancinating pain, burning, numbness, allodynia, and the presence of paresthesia or dysesthesia. The primary difference between this study and studies showing positive benefit was the rate of dose titration. The clinical experience of the use of lamotrigine as an analgesic for neuropathic pain is mixed, as in reported clinical trials.

Lamotrigine is currently recommended as a second-line or third-line analgesic agent because of mixed clinical data and its side-effect profile. Lamotrigine should be administered at low dosages and titrated slowly to minimize the risk of skin rash, including the possibly fatal Stevens-Johnson syndrome. Current dosing guidelines for the treatment of epilepsy in both children and adults call for slow titration.[63] One author's suggestion for dose titration in patients with neuropathic pain, on the basis of his clinical experience, is to initiate therapy at 50 mg/day and increase the daily dose by 50 mg each week until satisfactory analgesia is achieved.[111] Doses of up to 600 mg/day may be necessary for analgesia to occur in some patients,[110] and thus, it may take up to 12 weeks to titrate to meaningful effect.

Topiramate Topiramate is an anticonvulsant with multiple possible pharmacologic actions, such as sodium and calcium channel blockade and γ-aminobutyric acid (GABA) receptor activation. Early research in animal models indicates that this agent holds promise as a possible treatment of neuropathic pain conditions.[117] A case report of the successful treatment of a patient suffering from refractory postthoracotomy intercostal neuralgia suggests that topiramate may be useful in patients with neuropathic pain and illustrates the need for continued study to determine the efficacy and tolerability of this agent for the treatment of neuropathic pain.[118]

Anticonvulsants will continue to have an integral role in the management of neuropathic pain. Although in clinical practice these drugs have been used primarily for stabbing or lancinating neuropathic pain, studies have clearly shown that they can also alleviate burning, tingling types of neuropathic pain.

Newer agents with improved side-effect and drug-interaction profiles may provide the clinician with a broader array of choices to manage various types of neuropathic pain. As study design improves and future research emerges, the way in which anticonvulsants are chosen may change. Gabapentin is considered by many to be one of the first-line choices in the anticonvulsant therapeutic class because it has a better side-effect profile than the other agents and because of the strength of study design in trials involving patients with diabetic neuropathy and postherpetic neuralgia. For many clinicians, carbamazepine is still the first drug of choice for trigeminal neuralgia.

Topical Analgesic Agents

Although, in the United States, patients frequently utilize topical agents in OTC cream and gel formulations, physicians and patients have been relatively unaware of the fact that potent prescription analgesics are available as topical agents. The clinical advantages of topical drug delivery are many, including noninvasive ease of use, minimal risk of systemic side effects or drug-drug interactions, and the potential for use as monotherapy or as a complement to other agents. In recent years, the topical route of administration has gained popularity as a means of delivering pain relief locally; it is likely that this trend will continue to grow, given the successful treatment outcomes experienced by pain sufferers. Although topical analgesic agents do not represent a fourth class of analgesics (i.e., NSAIDs and adjuvants are available in topical formulations, commercial or otherwise), the topical route of administration and the agents currently available are notable and hence warrant highlighting.

Topical drugs are applied to the skin at the site that overlies the painful region of the body. The drug penetrates the skin and acts on the peripheral tissues, nerves, and soft tissues directly underlying the skin. The rate of delivery of the active medication can be well controlled through use of the optimal vehicle for topical drug delivery and use of the optimal matrix controls. The ideal topical formulation would achieve local concentration sufficient to produce a local effect without producing clinically relevant systemic blood levels. (A comparison of the properties of topical and transdermal drug delivery systems is presented [*see Table 9*].) Excessive drug absorption may cause local specificity to be lost, allowing a drug to be distributed systemically to undesired sites.

Recently, renewed attention has focused on topical products for the treatment of a variety of pain states (e.g., neuropathic pain and the pain associated with soft tissue injury).

Lidocaine 5% patch In 1999, the lidocaine 5% patch became the first drug to be approved by the FDA for the treatment of postherpetic neuralgia and the first true topical patch to be approved. The effectiveness of local anesthetics such as lidocaine is

Table 9 Comparison of Topical and Transdermal Drug Delivery Properties[86]

Characteristics	*Topical*	*Transdermal*
Application site	Directly on affected skin area	Any skin site (as drug needs to reach bloodstream to be distributed to affected tissue)
Target site	Local	Systemic
Serum drug concentration	Insignificant	Required
Systemic levels required for therapeutic effect	No	Yes
Titration required	No	Yes
Systemic side effects	No	Yes
Drug-drug interactions	No	Yes

believed to result from their ability to bind to sodium channels that are abnormally present and active on damaged nociceptors. When bound to these sodium channels, lidocaine reduces the abnormal ectopic discharges produced by damaged and dysfunctional peripheral nerves and interrupts conduction of the pain signal, thus alleviating pain. A topical patch preparation is currently available as a 10 cm × 14 cm nonwoven, polyethylene patch containing 5% lidocaine.

Three randomized, vehicle-controlled studies demonstrated that the topical lidocaine patch is efficacious and that it has no systemic activity and thus no systemic side effects.[119] The lidocaine patch was shown to be effective in alleviating all pain qualities associated with neuropathic pain; such pain qualities included burning, aching, shooting, and deep pain, as well as skin sensitivity and the presence of allodynia. Use of the lidocaine 5% patch does not result in altered skin sensitivity (i.e., numbness). Thus, the patch is analgesic but not anesthetic, unlike the topical local anesthetic cream preparation EMLA (eutectic mixture of local anesthetics).

The lidocaine 5% patch can be used as first-line treatment of postherpetic neuralgia.[120,121] The value of this approach for the treatment of other peripheral neuropathic conditions such as peripheral neuropathy, neuroma pain, and CRPS has yet to be determined through randomized, controlled trials. However, reports of the effectiveness of the topical lidocaine patch in the treatment of a variety of peripheral neuropathic pain conditions have been published.[122] In addition, a recent report noted its benefits in treating low back pain.[123]

Patients should use up to three patches to cover most or all of the painful region. The patches are applied directly to the painful area (the skin must be intact) and worn for 12 consecutive hours, after which they should be removed and discarded; after removal of the patches, new patches should not be applied for a period of 12 hours. Mild and transient local skin reactions (erythema or edema) may occur in some patients. The average serum level (0.13 mg/ml) is one tenth the value required for therapeutic antiarrhythmic use. In a recent study, the use of four patches for 18 hours resulted in the same serum levels of lidocaine as those achieved with the use of three patches.[124] In a large, open-label trial, a majority of patients (66%) reported some relief within 1 week of treatment; 43% of those not reporting relief in week 1 began to experience relief by week 2.[125] Thus, it is recommended that at least 2 weeks of daily treatment be allowed for an adequate patient drug trial.

EMLA EMLA (lidocaine 2.5% and prilocaine 2.5%) is available in a cream vehicle and an anesthetic disk. EMLA has been approved by the FDA for use as a topical anesthetic on normal, intact skin for local analgesia but not for the treatment of any chronic pain. Unlike the lidocaine 5% patch, EMLA produces anesthesia (i.e., numbness). A controlled trial in which EMLA was used to treat neuropathic pain associated with postherpetic neuralgia failed to show that EMLA was superior to placebo.[126]

Capsaicin Capsaicin is a natural substance derived from the chili pepper. Because capsaicin is a natural substance, the FDA has not investigated the formulations of this compound with as much scrutiny as it would a prescription drug. It is thought that capsaicin's analgesic activity results from desensitization through the depletion of substance P, a pain mediator, from sensory nerve endings. A recent in vitro study demonstrated that application of capsaicin results in neuronal death.[127] Results from controlled trials have been mixed with regard to the use of capsaicin for the treatment of neuropathic pain.[121] Many earlier controlled trials were flawed because they were not blinded with regard to the burning caused by application of capsaicin in a majority of persons. In a randomized trial that utilized an active placebo (i.e., an inactive substance that also causes some burning sensation upon application) in painful neuropathy, there was no statistical evidence that capsaicin cream was more efficacious than placebo for any of the trial's pain indices.[128] Besides its questionable efficacy, a major drawback of capsaicin is that it is poorly tolerated by many patients with pain (substantial burning pain may be experienced upon application).

NSAIDs Although topical NSAIDs are available in Europe, none are commercially available for use in the United States. Topical NSAIDs are prepared extemporaneously by pharmacists for individual patients when ordered by a health care professional with prescriptive authority. A recent review of relevant randomized trials was performed to determine the safety and effectiveness of topical NSAIDs for the treatment of acute and chronic pain. The relative benefit of such NSAIDs for acute conditions was assessed after 1 week; for chronic pain, relative benefit was assessed after 2 weeks. Treatment was considered successful if the patient experienced a reduction in pain of at least 50%. In at least three trials, ketoprofen, felbinac,

ibuprofen, and piroxicam showed significant efficacy in acute conditions (soft tissue trauma, strains, and sprains). In these placebo-controlled trials, the relative benefit was determined to be 1.7 (1.5 to 1.9), and the number needed to treat was 3.1 (2.7 to 3.8). Similar results were achieved in placebo-controlled trials involving patients with chronic pain (i.e., patients with osteoarthritis or tendinitis). The low incidence of side effects (both local and systemic) and the incidence of withdrawal from trials secondary to adverse drug effects did not differ from those experienced by patients receiving placebo. Topical NSAIDs have been demonstrated to be effective in the treatment of acute- and chronic-pain conditions. Further study will aid in determining the efficacy of other NSAIDs and will further help clinicians make rational, evidence-based decisions with regard to the use of topical NSAIDs.[129]

Evolving Pain Therapy

Our understanding of the underlying pathophysiologic changes that occur in chronic-pain states is rapidly growing. Over the past decade, it has become apparent that the entire nervous system undergoes adaptive (or "maladaptive") alterations in response to pain. These alterations are caused either by inflammatory changes or by dysfunction resulting from nervous system damage (i.e., so-called neuroplastic changes).[130,131] Neuroplastic changes occur throughout the nervous system—from peripheral nerve end-terminal to the spinal cord dorsal horn to the thalamus and cortex—and involve alterations in receptor and ion channel affinities and expression, electrophysiology, and transmitter and neuropeptide expression.[132] Remodeling, which occurs in damaged neurons in the form of increased expression of ion channels (e.g., sodium channels), has provided new strategies for drug development.[133] Receptors for NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) have been identified as playing key roles in the development of hyperalgesia and opioid tolerance.[131] New understanding of the roles of previously identified mediators, such as nitric oxide, in pain management is also leading to new treatment approaches.[134] Although a complete review of new therapeutic modalities is beyond the scope of this subsection, several particular therapeutic agents are worth a closer look.

The NMDA receptor complex has been shown to be involved in the development of central sensitization and opioid tolerance, even in the absence of opioid therapy.[135] A number of products currently marketed for other purposes are known to have activity at this receptor site. These products include dextromethorphan, ketamine, amantadine, and memantine. Methadone and dextropropoxyphene have partial blocking activity at the NMDA receptor, which may account for some of their efficacy.[136] Published research can be divided into two broad categories: (1) those studies aimed at showing decreased hyperalgesia and allodynia[131] and central sensitization and (2) those aimed at improved or enhanced analgesia (effected through combining these agents with opioid analgesics). The combining of NMDA receptor antagonists with opioid analgesics is believed to reduce tolerance and enhance the efficacy of the opioid at lower doses. The two most-studied agents are dextromethorphan and ketamine.

Dextromethorphan, which is commonly used as an antitussive, has been studied for its efficacy in painful peripheral neuropathy in rats.[135,137] In human trials, dextromethorphan has been studied for its usefulness in patients with diabetic neuropathy,[138] mixed neuropathic pain,[139] postherpetic neuralgia,[138,140] and cancer pain.[141] The results have been mixed; however, the negative results seen in some of these trials may have been the result of inadequate dosing.[136]

Ketamine has been studied for its usefulness in a number of pain conditions, including preemptive analgesia before appendectomy in pediatric patients,[142] cancer pain,[143,144] glossopharyngeal neuralgia,[145] postherpetic neuralgia,[146,147] and phantom limb pain.[148]

Although injectable ketamine has been shown to be effective for the treatment of pain in these settings and others, the primary limitation of the use of injectable ketamine has been its side-effect profile. The side effects include dissociative reactions, hallucinations, sedation, dizziness, nausea, and vomiting. A number of studies examined the use of ketamine administered via the oral route[134,149] and the topical or transdermal route[150]; when administered in these ways, ketamine was found to be efficacious and to have reduced side effects.

One method of enhancing analgesia that is currently under examination is the combination of low doses of an NMDA antagonist and low doses of opioid. This combination should result in a decrease in the development of opioid tolerance and a concomitant enhancement of analgesia.[136] Although dextromethorphan alone is not beneficial, in animal studies in which dextromethorphan was combined with morphine, the antinociceptive capabilities of morphine were potentiated,[151] with a resultant decrease in the development of tolerance.[152,153] Outcomes associated with the use of opioid-enhanced analgesia include improved pain relief, a reduction in the development of opioid tolerance, and opioid-sparing effects (i.e., the same analgesic response was achieved with lower doses of opioid). Two recent double-blind, multiple-dose studies evaluated the effectiveness of the combination of morphine and dextromethorphan (the two drugs were combined in a one-to-one ratio) in 321 patients with cancer pain and chronic pain. Patients who received the combination experienced significantly better pain relief than those who received the equianalgesic dose of morphine alone; the patients receiving the combination also experienced a faster onset of action and a longer duration of action.[154] In addition, the patients receiving the combination therapy required significantly less upward titration of morphine over time and significantly less amounts of morphine a day to achieve satisfactory pain control.

As researchers continue to search for new compounds with NMDA activity and new analgesic combinations that include NMDA antagonists, it is likely that these agents will have an integral role in pain management in the near future.

The depth of neuropathic pain research is not limited to compounds with NMDA activity. Two additional anticonvulsants are being examined for their potential usefulness in the treatment of neuropathic pain syndromes.[155] In initial clinical trials, pregabalin, a synthetic GABA analogue that has a mechanism of action similar to that of gabapentin, was shown to be effective in the treatment of painful diabetic neuropathy and postherpetic neuralgia. A second anticonvulsant, tiagabine, is being evaluated in animal models; it too appears promising. It is thought that antinociception induction occurs as a result of enhancement of GABA-mediated inhibitory neurotransmission. Ziconotide, another drug under investigation, is derived from marine snail venom; it is believed to block neurotransmitter release at the primary afferent nerve terminal via voltage-sensitive calcium channels. A toxin isolated from South

American tree frogs, epibatidine, has been classified as a nicotinic receptor agonist and has been demonstrated to cause analgesia in rats.[156]

Continued research and elucidation of pathophysiologic pathways are facilitating drug design targeted for specific underlying processes. Clinicians will soon have a plethora of novel pharmacologic agents from which to choose in treating specific pain syndromes.

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CHAPTER 87

Topical Medications

Bradley S. Galer

BASIC INFORMATION

Topical medications (Table 87-1) are applied directly on the painful body area, where they penetrate the skin. A topical medication's site of activity is in the peripheral tissues, including soft tissue and peripheral nerve, directly underlying the site of application. Topical drugs, formulated as a gel, cream, liquid, or patch, should not produce any clinically significant systemic drug concentration.

Transdermal medications, on the other hand, are also applied directly to the skin, but the site of drug application can be distant from the area of pain (currently available transdermal drugs include fentanyl and clonidine). Transdermal drugs' sites of activity are not local but via a systemic effect. The medication of transdermal delivery systems is typically contained in a pooled reservoir within a patch, which is designed to push drug directly into the bloodstream. Therefore, unlike topical medication patches, a transdermal patch cannot be cut into different sizes.

Therefore, the key difference between topical and transdermal drug delivery systems is that a topical medication does not result in any clinically meaningful blood levels, whereas a transdermal drug must result in clinically effective serum concentrations for its clinical effect.

History

Applying medicinal substances directly on the skin is likely one of the oldest routes of administration. Ancient cultures ground herbs and plants into pastes for medical uses, including the treatment of pain. Over the past century, many tonics, gels, salves, and lotions have been sold as over-the-counter remedies for pain, although most have little to no scientific study to back their claims (e.g., "snake oils"). Many of these older topical medicinal products may in fact act only as counterirritants—that is, they produce a mild to moderate noxious stimulus that then suppresses the perception of the pain.

Only in the past few decades has the pharmaceutical industry begun to develop topical drugs for the treatment of pain with the aim of producing products with proven efficacy. However, even at the time of this writing, the commercial availability of topical pain medication with controlled clinical trial evidence of efficacy remains sparse. Yet, much development and clinical trial study are currently under way, with the promise of safe and effective topical drugs for the treatment of many acute and chronic painful conditions.

Theoretical Bases

Mechanisms of Action

Because topical drugs, by definition, must act locally on dysfunctional or damaged soft tissues or peripheral nerves, all abnormal pathophysiologic events within the periphery that generate or maintain pain are potential targets for these medications. In acute pain syndromes and arthritic conditions, topical drugs may play a role in reducing the inflammatory response and concurrent sensitization of nociceptors. In chronic neuropathic pain, abnormal neuronal activity abnormal impulse generation secondary t sodium channels or α-adrenergic receptors is a p as is the ongoing neurogenic inflammatory resp

Clinical Advantages

Theoretically, topical drugs' activity should b of pain generation, unlike oral and other systemic need to enter the bloodstream before they arrive site of action. Therefore, because topical drugs any clinically significant serum levels, adverse re ited to those produced by local reaction, such a rash. Most of the currently prescribed oral and tr ications for pain, both acute and chronic, are ha systemic side effects. With nontopical agents, it is essary to titrate the dosage to effect, either pain r ble side effect; unfortunately, the latter often oc an aborted drug trial and the patient still sufferir

Another advantage to topical agents is the drug interactions, again due to their lack of s The potential for drug-drug interactions is co patients with chronic painful conditions, such with arthritis or postherpetic neuralgia (PHN) fering from painful neuropathies, such as diab immunodeficiency virus (HIV) patients.

When treating chronic pain conditions, trea agents requires slowly titrating the dose until pain relief or intolerable side effects are reported time-consuming procedure that may take weeks The time to a noted effect with topical agents, o usually is on the order of days. Thus, yet anot topical drugs is the significant amount of time sa to titrate the dose over several weeks or more.

An additional important advantage of topi ease of use. Patients either need to apply a liqu several times a day or, with some preparation once or twice a day.

Clinical Information

Indicated Pain Conditions. Clinical cond with pain in which a topical agent may have include both acute and chronic pain states. Acu suitable for topical pharmacotherapeutic int acute soft tissue injuries (e.g., sprains, strains, postsurgical pain, and acute herpes zoster (s nonmalignant pain states appropriate for topic include arthritic conditions and chronic perip pain conditions, such as PHN, diabetic poly neuropathy, idiopathic neuropathy, complex r dromes, stump pain, and other neuroma pains.

Medication Classes. Currently only a fe mercially available for the treatment of pain, in dal antiinflammatory agents, capsaicin, and loca However, several new topical drugs—using di

BLE 87-1. Topical versus transdermal drug delivery

	Topical	Transdermal
tion site	Skin: directly on painful skin	Skin: distant from painful region
ctivity	Peripherally (soft tissue, nerve)	Systemically
rug concentration	Insignificant	Necessary
c side effects	No	Yes
needed	No	Yes
ug interaction	No	Yes

ns, with a new active medication ingredient, or both—are being investigated (at the time of this writing), and it is hat they will prove efficacious in the not too distant future reatment of a variety of acute and chronic pain conditions. eral different topical formulations may be available the same medication class, which may differ signifi- with regard to efficacy and side effect profile. Such dif- topical drugs in the same class may differ in several ly significant ways, including (a) the actual active medi- being delivered; (b) the topical vehicle formulation's ents, which affect skin penetration and drug delivery; the application form in which the drug is available, such d, gel, salve, or patch/plaster. Each of these three factors tly important relevance with regard to the topical drug's and adverse events (Table 87-2).

GS

eroidal Antiinflammatory Drugs

ll of the drug classes, the nonsteroidal antiinflammatory NSAID) class has the most studied and currently avail- able different topical drug formulations that are commercially available or under investigation. Many different NSAIDs with vastly different vehicle formulations have been assessed in mostly acute pain syndromes and arthritic conditions.

Mechanism of Action

NSAIDs traditionally have been thought to have their primary mechanism of analgesic activity in the periphery, specifically via their inhibition of prostaglandin synthesis. However, a dissociation between the degree of pain relief of certain NSAIDs and their actual antiinflammatory effects suggests other important analgesic mechanisms of activity (1), including other peripheral effects, such as inhibition of the lipoxygenase pathway, inhibition of excitatory amino acids, and effects on G protein–mediated signal transduction (2).

Topical NSAIDs may also have direct effects on damaged and dysfunctional peripheral nerves. Topical NSAIDs theoretically could reduce primary afferent sensitization occurring as part of a localized abnormal neurogenic inflammatory response (3). An animal study of rabbit corneal nerve injury reported a significant reduction of abnormal neural activity and mechanosensitivity after application of topical diclofenac (4).

Clinical Trial Data

Acute Pain. Topical NSAID treatment has been studied for several clinical conditions associated with acute pain, including minor sports injury pain, postsurgical pain, and ophthalmic pain. A multicenter, randomized, double-blind, placebo-controlled study of acute sports injury pain found significant reductions of pain over a 2-week period with a diclofenac patch/plaster (5). An open-label study observed a 60% reduction in pain with this diclofenac patch/plaster in traumatic sport and overload injuries (6). Similar controlled studies in acute soft tissue injuries revealed significant reductions in pain over the first 48 hours with an ibuprofen cream (7) and over 7

TABLE 87-2. Controlled and uncontrolled studies assessing the efficacy of topical drugs for the treatment of pain

		Arthritic pain (c/uc)		Acute pain (c/uc)		Neuropathic pain (c/uc)		
g class	Agent	Rheumatoid arthritis	Osteoarthritis	Soft tissue	Postsurgical	Acute herpes zoster	Postherpetic neuralgia	Diabetic neuropathy
	Diclofenac patch/ plaster		+/	+/+				
	Diclofenac gel			/+				
	Diclofenac with hyaluronan		+/					
	Diclofenac with ether					+/+*	+/+*	
	Ibuprofen cream			+/				
	Ketoprofen gel			+/+				
	Piroxicam gel							
	Eltenac gel		+/		+/			
	Aspirin/ether		+/		+/	+/+*	+/+*	
esthetic	Lidocaine							
	Lidoderm patch						+/+	–/+
	Lidoderm gel						+/+	–/+
	Lidocaine/prilocaine							
	EMLA cream			+/**			–/	
	EMLA patch			+/**				
n		M/	+/		+/		M/M	M/M
ne	Gel				+/		/+	/+

ontrolled study(ies); EMLA, eutectic mixture of local anesthetics; M, mixed results; NSAIDs, nonsteroidal antiinflammatory drugs; uc, uncontrolled study(ies) dotal report(s); +, positive results; –, negative results; *, single-session studies; **, pain associated with venipuncture, biopsy, and circumcision.

days with ketoprofen gel (8). An open-label uncontrolled study comparing several different topical gels for acute soft tissue injury pain observed that diclofenac gel and ketoprofen gel were similar in efficacy, whereas piroxicam gel was less effective (9).

A double-blind comparative study assessed piroxicam gel applied preoperatively to patients undergoing an inguinal repair, local anesthetic inguinal block, and no treatment and reported that both the topical NSAID gel and the nerve block similarly reduced pain scores, time to first analgesic, and total opiate consumption as compared to the no-treatment group (10). Double-blind controlled studies have assessed topical NSAIDs for the treatment of acute pain associated with traumatic corneal abrasions and found significant reductions in pain (10–12). A study has also reported significant pain reduction with topical diclofenac treatment for postoperative pain associated with phototherapeutic keratectomy (13).

Arthritic Pain. A large randomized, multicenter, double-blind, 4-week study compared topical eltenac gel with oral diclofenac and placebo in patients with osteoarthritis of the knee and found that both active treatments were significantly better than placebo in reducing pain only in patients with severe symptoms, but that the number of gastrointestinal adverse reactions were three times higher in the oral NSAID group as compared to the topical NSAID group (14). Controlled studies demonstrated efficacy of a topical diclofenac in hyaluronan for the treatment of osteoarthritis (15–17). Placebo-controlled studies have reported significant reductions in pain with topical diclofenac plaster (patch) in patients with osteoarthritis of the knee (18), and inflammatory peri- and extraarticular rheumatologic diseases (19). After several days of diclofenac plaster application in patients with monolateral knee joint effusion, low levels of diclofenac were measurable in the synovial fluid without producing elevated serum levels (20). An open-label uncontrolled study reported topical flurbiprofen patches provided significantly better pain control as compared to oral diclofenac with significantly fewer gastrointestinal side effects after 2 weeks of treatment in patients with "soft-tissue rheumatism" (21).

Neuropathic Pain. A single-session, double-blind, crossover study reported significant pain reduction for the treatment of both acute herpes zoster and PHN with a topical diclofenac/diethyl ether mixture with no significant side effects (22). This same study reported that an indomethacin/diethyl ether topical mixture was not superior to placebo in a single-session protocol. Another single-session study observed significant pain reduction in patients suffering from PHN with hydrous stupes (topical patches) containing indomethacin, ketoprofen, or flurbiprofen (23). However, no long-term efficacy studies with topical NSAIDs have been published for the treatment of either acute herpes zoster or PHN. No studies have assessed the use of topical NSAIDs for other peripheral neuropathic pain conditions.

Aspirin

Although no commercially produced form of topical aspirin is available at the time of this writing, several studies have reported the results of compounded formulations of topical aspirin for the treatment of pain associated with herpes zoster.

Mechanism of Action

Like the topical NSAIDs, topical aspirin may alleviate pain by affecting the inflammatory response and, at least theoretically, in neuropathic pain states by reducing neurogenic inflammation.

Neuropathic Pain

A double-blind, placebo-controlled, single-session clinical [illegible] statistically significant pain relief in patients with acute herpes zoster and PHN after application of a topic aspirin/diethyl mixture (24). In addition, several open-lab studies have described pain reduction in PHN using topic mixtures of aspirin and chloroform or diethyl ether (25,26). N controlled study has assessed the long-term benefits and sic effects with topical aspirin formulations.

Local Anesthetics

Over the past decade, two commercially produced forms topical local anesthetics have extensively undergone the rigors placebo-controlled clinical trials testing, Lidoderm gel ar patches and EMLA (eutectic mixture of local anesthetics, 2.5 lidocaine and 2.5% prilocaine) cream and patch. To date, bc products have proven efficacy for different clinical pain stat Lidoderm for peripheral neuropathic pains and EMLA for acu pains associated with invasive procedures, such as venipunctu Other topical formulations of local anesthetics have also b reported for the treatment of acute pain states.

Mechanism of Action

Local anesthetic drugs applied topically are thought to p vide pain relief by reducing ectopic discharges in superfi somatic nerves, which are damaged and dysfunctional in r ropathic pain states and are normally active in acute inju such as venipuncture. It is not necessary to produce a anesthesia of the skin to produce clinically significant relief in chronic neuropathic pain states. Animal models of ropathic pain have shown significant reductions in the at mal tonic, evoked, and ectopic activity in damaged perip nerve with local anesthetic concentrations dramatically b that which blocks impulse conduction (27,28). In additi topical patch, such as the Lidoderm patch, has been sho have an added benefit of protecting allodynic skin from mechanical stimulation and thereby of reducing an allo patient's pain (29,30).

Neuropathic Pain

A large multicenter, placebo-controlled, double-blind reported significant pain relief with 4 weeks of lidocaine (Lidoderm) use in patients with long-standing PH mechanical allodynia (30). Another controlled trial in using an enriched enrollment crossover design, demon that long-term lidocaine patch users (mean duration o use was 3.3 years; mean duration of PHN 7.3 years) pr the lidocaine patch to the placebo patch, 78% versus 9% ((31). In addition, several double-blind, placebo-controll gle-session studies have reported Lidoderm, both the patch formulations, to be effective in significantly redu pain of PHN without any significant side effects Lidocaine serum levels after use of this gel and the p mulation are an order of magnitude below antiarr serum levels and are thus very safe, even in patients diac conditions (29,30,33).

A randomized controlled trial of topical lidocaine patches for the treatment of painful diabetic ne showed clinically significant reductions in pain with active and placebo treatments in the vast majority o but no statistical difference between the two treatme BS, Gianis A, *unpublished results*, 1988). Of interest majority of subjects in this study continue to use the patch or gel in a compassionate use protocol with meaningful reductions in pain, even if they respon placebo treatment in the controlled study. Anecdota also suggests this drug may be useful for the treatme peripheral neuropathic pains, such as idiopathic po thy, painful mononeuropathy, stump pain, reflex s dystrophy, and painful HIV neuropathy (35,36).

Long-term efficacy appears to be maintained for this new ›pical lidocaine preparation. PHN and diabetic neuropathy atients who have applied Lidoderm for several years report ›ntinued pain relief, with some patients noticing a decrease in ıe size of the painful region and others needing to apply the ›pical medication less and less frequently. No significant acute ·chronic side effects have been observed.

The other commercially available formulation of topical :al anesthetic, EMLA, has failed to demonstrate efficacy supe›r to placebo (37).

:ute Pain

Controlled studies have reported EMLA cream applied ıder an occlusive dressing for 60 minutes reduces pain associ›d with venipuncture (38,39), intramuscular saline injections)), spinal needle insertion (41), excisional biopsy or curettage th electrosurgery of cutaneous lesions (42), and pain from cirmcision in neonates (43). A patch impregnated with EMLA ıs also shown to reduce pain associated with a skin biopsy in ldren (44) and venipuncture pain in adults (45).

A controlled comparative study of volunteers undergoing ravenous catheterization reported that liposome-encapsu›d tetracaine provided more effective pain relief than EMLA am after 60 minutes' application time, although the tetrane also caused more erythema than the EMLA (46). Topical ›paracaine was shown in a double-blind study to reduce the n after photorefractive keratectomy (47). A double-blind dy reported equally effective pain reduction with the use of ical bupivacaine-adrenaline-cocaine and topical tetracaineenaiine-cocaine mixtures for pain associated with wound ıring (48). A double-blind study assessed the efficacy of topilocal anesthetics for pain associated with suturing lacerations hildren and concluded that topical prilocaine-phenylephrine ; tetracaine-phenylephrine (tetraphen) was as effective as cal tetracaine-adrenaline-cocaine (49).

›saicin

:hanism of Action

'apsaicin is an over-the-counter drug composed of an ıct of chili peppers. It has been postulated that capsaicin :tively stimulates and then depletes substance P from nociive primary afferents and thus may produce pain relief in ıin chronic pain states. However, this physiologic activity ıot been definitively proved to be the mechanism of action ırrently available capsaicin products. An animal study of rimental polyarthritis has noted that pretreatment with ıicin significantly attenuated joint swelling and radiologic histologic measures of arthritic changes, suggesting that ıicin may directly suppress inflammation (50). Moreover, ıicin produces a counterirritant effect in a majority of nts by causing a mild to severe burning on application, ı may also be a potential therapeutic pain mechanism. use of this commonly occurring burning on application, bo-controlled trials of capsaicin should be interpreted caution since both subject and researcher are unblinded this occurs.)

›pathic Pain

›ical capsaicin has been studied in PHN and painful dianeuropathy with mixed results. In PHN, several studies reported reductions in pain (51–54), whereas others have ı). Similarly, controlled studies in painful diabetic neuropave also resulted in both negative and positive findings. A mized controlled trial of 0.075% capsaicin in painful dianeuropathy showed no benefit (55). Another controlled using 0.075% capsaicin in painful diabetic neuropathy reported improvement in pain with capsaicin, although an intent-to-treat analysis was not performed (56). A controlled trial using an active placebo (a topical substance that also produced burning on application but had no pain-relieving capabilities) reported no difference between capsaicin and this active placebo in patients with a variety of painful polyneuropathies (57). One small controlled study reported topical capsaicin reduced the pain of postmastectomy syndrome (58).

Unfortunately, currently available formulations of capsaicin have been disappointing clinically as an analgesic agent for all neuropathic pains (59). Currently, most authorities rarely prescribe the drug for the treatment of neuropathic pain due to its overall poor efficacy and the high proportion of patients who complain of a worsening of their pain with drug application.

Arthritis Pain

Two controlled studies have demonstrated efficacy and safety for the use of topical capsaicin in the treatment of arthritis pain. A small double-blind, placebo-controlled study concluded that capsaicin significantly reduced hand pain from osteoarthritis but not pain from rheumatoid arthritis (60). However, a large double-blind study of arthritic knee pain reported significant pain relief in both rheumatoid arthritis and osteoarthritis, with more relief reported by rheumatoid arthritis subjects (61).

Clonidine

At the time of writing, no topical clonidine product is commercially available. However, a new formulation of a topical clonidine gel is being studied for a variety of neuropathic pain states.

Mechanism of Action

Clonidine is an α_2-adrenergic partial agonist. Alpha-2 receptors are autoreceptors located on the sympathetic nerves' terminals, which when activated inhibit their release of norepinephrine. Several lines of evidence suggest an abnormal adrenergic sensitivity in peripheral neuropathic pain states. For instance, locally infused adrenaline results in a worsening of pain and allodynia patients with reflex sympathetic dystrophy (62) and PHN (63). In addition, animal models of peripheral neuropathic pain have shown that injured neurons are sensitive to adrenergic activity, that is, an increase in ectopic impulse generation occurs in response to sympathetic agonists and to activation of postganglionic sympathetic efferent axons (64). Moreover, this adrenosensitivity appears to be an inherent property of the injured somatic peripheral nerve (65). Thus, application of clonidine topically may reduce release of norepinephrine from sympathetic nerve terminals, thereby alleviating the abnormal ectopic firing resulting from the dysfunctional nerve's adrenosensitivity, and, at least theoretically, result in clinically meaningful reductions in pain and allodynia.

Neuropathic Pains

No controlled studies have been performed using a topical form of clonidine, at the time of this writing. However, uncontrolled pilot studies have been performed assessing different concentrations of this new formulation of topical clonidine gel for the treatment of PHN, complex regional pain syndrome type I, and painful diabetic neuropathy. These open-label studies have observed improvement in pain and hyperalgesia in some patients (66). Controlled trials with topical clonidine gel are being planned.

One uncontrolled case series assessed the efficacy of transdermal clonidine patch (Catapres) in four patients with "sympathetically maintained pain" and two with "sympathetically independent pain" (67). This series observed that the patients with sympathetically maintained pain obtained complete relief

of hyperalgesia only in the localized skin region under the patch but no change in the spontaneous ongoing pain, whereas no pain relief at all was noted by the two patients with sympathetically independent pain.

CONCLUSIONS

Theoretically, topical drugs have many clinically relevant advantages over other pharmacotherapeutic drug delivery systems, such as oral, transdermal, and intrathecally delivered drugs. By applying a drug directly to the skin, where it penetrates and acts directly at a site of pain generation without the need for systemic activity or invasive procedure, topical medications have the promise of producing pain relief with few side effects and little risk and cost. In the past, the question plaguing topical drug delivery has been whether clinically meaningful degrees of pain relief can be achieved with topical administration. Controlled clinical trials have demonstrated efficacy for a variety of topical drugs and topical formulations, such as NSAIDs, in topical treatment of acute soft tissue injury and arthritis and in topical anesthetics' treatment of chronic peripheral neuropathic pain states. The treatment of acute pain associated with invasive procedures. The many newer topical books bright for topical drug delivery, with both acute and chronic agents being studied for the treatment of pain conditions. Because of their efficacy, safety, quick onset, and ease of use, topical medications should be considered first-line agents for the treatment of many pain states.

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